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(54) Title: USE OF PHARMACEUTICAL COMPOUNDS IN THE TREATMENT OF SYMPTOMS OF DISORDERS RELATED TO NEUROLOGICAL DISEASES AND ETIOLOGICALLY RELATED SYMPTOMOLOGY

(57) Abstract

The invention regards a novel use of pharmaceutical compositions in treating symptoms of disorders relating to neurological diseases and for treating pathophysiologically related symptomology in other body tissues, including peripheral neuropathies, secondary symptomology of diabetes, Alzheimer's disease, Parkinson's disease, alcoholic polyneuropathy and age-onset symptomology. Covalent bond crosslinking of protein and lipid subcellular elements appears to underlie the formation of polymerized aggregates of neurofilaments, other structural proteins and lipofuscin. The use of certain compounds may compete with cellular protein and lipid amine groups for reaction with disease-induced carbonyl-containing aliphatic and aromatic hydrocarbons. Such derivatized pharmacological agents can then be excreted by the kidneys, thus removing the toxic agent(s). The presence of an acid functional group on the agent used facilitates kidney recognition and removal. Another application of the present invention includes the oral use of non-absorbable polyamine agents and amine-related agents such as chitosan and cholestyramine to covalently bind and sequester potentially toxic carbonyl compound present in the diet. Veterinary, food processing and cosmetic applications of the present invention are also described.

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USE OF PHARMACEUTICAL COMPOUNDS IN THE TREATMENT OF SYMPTOMS OF DISORDERS RELATED TO NEUROLOGICAL DISEASES AND ETIOLOGICALLY RELATED SYMPTOMOLOGY

I. SUMMARY OF THE INVENTION

The present invention is directed to the use of a water soluble, low molecular weight substance containing a primary amine group or amine-related group, for use in the treatment of symptoms of disorders based on neurofilament associated pathology and/or pathophysiologically related symptomology.

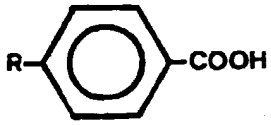
In a preferred embodiment, the use of a water soluble, low molecular weight substance in the range of 100 to 1,100 is selected from the group consisting of free acid forms, salts, benzene ring isomers, amide derivatives, carboxylic acid ester derivatives and sulfonic acid ester derivatives of the group consisting of:

a. para-aminobenzoic acid (PABA);
b. para-aminomethylbenzoic acid and analogous derivatives of

the formula $H_2N-(CH_2)_n-C_6H_4-COOH$ where n = 2-30, including meta- and ortho-benzene ring isomers of the aminoalkyl group and isomers of the aminoalkyl group where the amine is not in the omega position;

c. 4-Amino-3-methylbenzoic acid and other derivatives of PABA or benzene ring isomers thereof wherein such derivatives include from one to four additional ring substituents from the group consisting of methyl group(s), ethyl group(s), or other hydrocarbon group(s) (up to 5 carbons); substituted -OH group(s) of the structure $-OCH_3$, $-C_2H_5$ or higher molecular weight ethers (up to 5 carbons); substituted amine group(s) of the structure -NHR, $-NR_2$ or -NHCOR where R is a hydrocarbon substituent such as $-CH_3$ or derivative thereof (R having 1 to 5 carbons);

d. 4-amidinobenzoic acid, $H_2N-C(=NH)C_6H_4-COOH$, and the following derivatives thereof:



where R= $-NHC(=NH)NH_2$
or $CH_2NHC(=NH)NH_2$
or $(CH_2)_nNHC(=NH)NH_2$
where n = 2 - 10;

e. para-aminophenylacetic acid and analogous derivatives of the formula $H_2N-(CH_2)_n-C_6H_4-CH_2-COOH$ where n = 1-30, as well as methyl and other sidechain hydrocarbon isomers of the amino-alkyl group, and/or hydroxylated derivatives of the sidechain amino-alkyl group, and/or derivatives bearing hydrocarbon or hydroxyl substitutions at the alpha carbon of the acetate group;

f. 4-amidinophenylacetic acid, $H_2N-C(=NH)C_6H_4-CH_2-COOH$;

g. para-aminohippuric acid, $H_2N-C_6H_4-CO-NH-CH_2-COOH$;

h. 3,5-diaminobenzoic acid and other benzene ring diamine isomers;

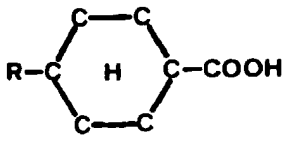
i. 3,5-diaminoalkylbenzoic acid and benzene ring isomers, where aminoalkyl is $H_2N-(CH_2)_n-$ and n = 1 - 30, including hydrocarbon isomers, or where aminoalkyl is $H_2N-(CH_2)_m-CHOH-(CH_2)_n-$ where m = 0 - 15 and n = 0 - 15, including hydrocarbon isomers thereof;

j. para-aminosalicylic acid, and the isomeric amine and hydroxyl derivatives thereof, as well as derivatives wherein the hydroxyl group has been replaced by a methoxy group or alkyloxy

group having 2-10 carbons;

k. 4-amino-2-sulfobenzoic acid, and derivatives thereof including benzene ring isomers and derivatives where the amino group is replaced by an aminoalkyl group having 1-10 carbons, and derivatives where the carboxylic acid group is replaced by a $-(CH_2)_n-COOH$ group (n=1-10);

l. tranexamic acid, 4-(aminomethyl)cyclohexane-carboxylic acid, and the ring positional isomers thereof, and derivatives



wherein R= $-NH_2$

$-(CH_2)_n NH_2$

where n=2-10

$-NHC(=NH)NH_2$

$-CH_2 NHC(=NH)NH_2$

$-(CH_2)_n NHC(=NH)NH_2$

where n = 2 - 10;

m. 6-aminonicotinic acid and the ring isomer derivatives thereof;

n. epsilon-aminocaproic acid, and analogous remaining derivatives of the formula $H_2N-(CH_2)_n-COOH$, where n = 1-30, including isomers wherein the amine is not in the omega position as well as derivatives wherein the alkyl group bears sidechain methyl or other hydrocarbon substitutions and/or hydroxyl group substitutions thereon;

o. 2,3-diaminopropionic acid and analogous derivatives of the formula $(H_3C)_a-CHNH_2-(CH_2)_b-CHNH_2-(CH_2)_c-COOH$ where a = 1 or 0 (in which case omega terminal group is H_2N-CH_2-), b = 0 - 30 and c = 0 - 30, including hydrocarbon isomers of (b) and (c), as well as hydroxylated isomers of (a), (b) and (c);

p. omega-aminoalkylsulfonic acids, $H_2N-(CH_2)_n-SO_3H$ where n = 1 - 20, such as 2-aminoethanesulfonic acid (taurine), including isomeric hydrocarbon derivatives and hydroxy or methoxy derivatives thereof;

q. omega-guanidinoalkylcarboxylic acids, of the general structure $H_2N-C(=NH)NH(CH_2)_n COOH$, where n=1-10;

r. 4-aminobenzenesulfonic acid (sulfanilic acid) and derivatives thereof, including benzene ring isomers such as 2-aminobenzene-sulfonic acid (or aniline-2-sulfonic acid) and

aminoalkyl-benzene-sulfonic acids, wherein the aminoalkyl is $H_2N-(CH_2)_n-$, n = 1-15, as well as derivatives having more than one amino- or aminoalkyl- group;

s. sulfanilamide, $p-H_2N-C_6H_4-SO_2NH_2$, including the metabolic precursor derivatives thereof such as 4'-sulfonamido-2,4-diaminoazobenzene hydrochloride and 4'-sulfonamido-2-benzeneazo-7-acetylamino-1-hydroxynaphthalene-3,6-disulfonic acid, and the 1-amino substituted derivatives such as sulfabenz, sulfabenzamide, sulfabromomethazine, sulfacetamide, sulfachlorpyridazine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamoxole, sulfanilamidomethanesulfonic acid, 4-sulfanilamidosalicylic acid, 2-p-sulfanilylanilinoethanol, p-sulfanilylbenzylamine, N^4-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfanitran, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfaquinoxaline, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfazamet, sulfisomidine, sulfisoxazole, and derivatives thereof,

for controlling the symptoms of disorders selected from the group consisting of hereditary motor and sensory neuropathies, giant axonal neuropathy, diabetic polyneuropathy and metabolic symptomology related thereto, Alzheimer's presenile dementia, Alzheimer's senile dementia, Down's syndrome, Pick's disease, Parkinson's disease, amyotrophic lateral sclerosis, and disorders clinically related thereto, Huntington's disease, tinnitus, spinal muscular atrophy, age-related atrophy of peripheral sensory and motor nerves, age-related atrophy of autonomic nerves including symptoms of hypoperistalisis of the alimentary tract, hiatal hernia (partial food regurgitation), urinary incontinence, breathing insufficiency due to diaphragm weakness and decreased autonomic sexual function, age-related atrophy of neurons of the central nervous system, age-onset pathophysiologically related changes in the cardiovascular system, kidney, optic lens and skin, including age-related skin wrinkling,

Friedreich's ataxia, alcoholic polyneuropathy, multiple sclerosis, ceroid lipofuscinosis, muscular dystrophy disorders and atherosclerosis.

In a preferred embodiment the water soluble low molecular weight substance is used in a dosage in the range of 600 mg/day to 40 grams/day.

In a preferred embodiment, the use of the substance is used orally.

In a preferred embodiment, the use of the substance is used intravenously.

In another preferred embodiment the use of the water soluble low molecular weight substance is used in combination with a co-agent.

In a preferred embodiment the co-agent is selected from the group consisting of antioxidants, suspending reagents or the functional equivalents thereto, vitamins, hormones, chemical conjugating agents which facilitate kidney drug elimination, metabolites at risk of depletion or free radical trapping compounds.

In a preferred embodiment, the antioxidant is selected from the group consisting of vitamin E (alpha-tocopherol), selenium, citric acid, ubiquinol, a seleno-containing amino acid, glutathione, sulfhydryl containing proteins, cysteine, homocysteine and methionine.

In a preferred embodiment, the suspending reagent is selected from the group consisting of carboxymethyl cellulose or functional equivalents thereof.

In a preferred embodiment the vitamin is selected from the group consisting of vitamin A, D, K and B-6.

In a preferred embodiment, the hormone is selected from the group consisting of human growth hormone.

In a preferred embodiment, the chemical conjugating agent which facilitates kidney drug elimination is selected from the group consisting of glycine and derivatives thereof.

In a preferred embodiment the metabolite at risk of depletion is selected from a group consisting of pantothenic acid and derivatives thereof.

In a preferred embodiment, the co-agent is a sulfhydryl-

containing agent or derivative thereof such as cysteine, homocysteine, methionine or thioctic acid (alpha-lipoic acid).

In a preferred embodiment, the co-agent is used orally.

In a preferred embodiment, the co-agent is used intravenously.

In another aspect of the invention, the invention relates to the use of a water soluble, small molecular weight, primary amine containing chemical agent or amine-related derivative thereof as defined above for controlling the symptoms of animal disorders featuring neurofilament associated pathology and/or pathophysiologically related symptomology.

Another aspect of this invention involves the use of a non-absorbable polyamine agent or non-absorbable polyamine-related agent or quaternary ammonium salt derivative thereof for use in the treatment of symptoms of disorders based on neurofilament associated pathology and/or pathophysiologically related symptomology.

In a preferred embodiment, the use of a non-absorbable polyamine agent or non-absorbable polyamine-related agent or quaternary ammonium salt derivative thereof is selected from the group consisting of:

a. any naturally occurring polysaccharide having beta-1,3, beta-1,4 and/or beta-1,6 linkages containing aminosugars including but not limited to the chitin class of biopolymers having the general structure of **poly-beta-(1→4)-N-acetyl-D-glucosamine** wherein such naturally occurring polysaccharide may be pretreated so as to create a microfibrillated form or microcrystalline form having enhanced surface area, increased water retention capacity and enhanced chemical accessibility such that said pretreated naturally occurring polysaccharides bear at least one free primary amine group and have a high porosity and enhanced susceptibility to chemical reactions;

b. deacetylated naturally occurring polysaccharides, having at least one N-acetylated residue, wherein upon chemical deacetylation thereof, said deacetylated naturally occurring polysaccharide is a high molecular weight derivative bearing primary amine groups directly linked to sugar carbons; including but not limited to chitosan, chondroitin sulfate, hyaluronic

acid and keratan sulfate;

c. chemically aminated polysaccharides including but not limited to:

2-amino-2-deoxy-cellulose and other aminodeoxy polysaccharides;

3-aminopropylcellulose;

aminoethylcellulose;

other aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether-, and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates including aminoalkyl derivatives such as

$H_2N-(CH_2)_n-$[carbohydrate] where n = 1 - 30, including alkyl isomers;

amino(hydroxyalkyl)- derivatives such as

$H_2N-(CH_2)_m-CHOH-(CH_2)_n-$[carbohydrate], where m = 0 - 15 and n = 0 - 15;

aminoalkyl-ether- derivatives and amino(hydroxyalkyl)-ether- derivatives such as $H_2N-(CH_2)_n-O-$[carbohydrate] where n = 1 - 30 and $H_2N-(CH_2)_m-CHOH-(CH_2)_n-O-$[carbohydrate] where m = 0 - 15 and n = 0 - 15;

aminobenzyl derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates such as

$$H_2N-C_6H_4-(CH_2)_n-[\text{carbohydrate}]$$

and $H_2N-CH_2-C_6H_4-(CH_2)_n-$[carbohydrate]

and $H_2N-C_6H_4-(CH_2)_n-O-$[carbohydrate] where n = 0 - 30

and $H_2N-C_6H_4-(CH_2)_m-CHOH-(CH_2)_n-O-$[carbohydrate]

where m = 0-15 and n = 0-15, including p-, o- and m-benzene ring amino- and aminomethyl- isomers, and alkyl group isomers thereof;

d. primary, secondary and tertiary amine and guanidine derivatives of sucrose polyesters including derivatives having one or more carbonyl trapping functional group wherein the carbonyl trapping functional group is in the omega-, omega-1 or other isomeric position(s) within the fatty acyl chains;

e. synthetic polysaccharides consisting partly or entirely of aminosugars bound by beta-1,3, beta-1,4 and/or beta-1,6 linkages;

f. primary amine containing non-polysaccharide polymers which are capable of reacting with dietary carbonyl compounds including but not limited to

cholestyramine;

Bio-Rad aminex resin products such as Aminex A-14, Aminex A-25, Aminex A-27 and Aminex A-28 which are quaternary amine derivatives of 8 % crosslinked styrene divinylbenzene copolymer resin;

colestipol;

other anion exchange resins with antihypercholesterolemic properties such as Secholex (also known as polidexide, DEAE-Sephadex or PDX-C1);

synthetic polymers having o-, m- or p-benzylammonium side chain functional groups;

and structurally related substances such as:

- weakly basic resins prepared by condensation of epichlorohydrin with ethylene imine, primary amines, secondary amines or diamines;
- other epichlorohydrin copolymers with cellulose, chitin or dextran having basic substituent functional groups such as $-OC_2H_4N(C_2H_5)_2$;
- other styrene-divinylbenzene copolymer anion exchange resins having quaternary ammonium functional groups such as $-CH_2N^+(CH_3)_3Cl^-$ or $-CH_2N^+(CH_3)_2CH_2CH_2OHCl^-$;
- styrene-divinylbenzene copolymer anion exchange resins having pyridinium functional groups;
- other styrene-divinylbenzene copolymer anion exchange resins having primary, secondary or tertiary amine functional groups;
- polystyrene resins having guanidine functional groups [e.g., $-NHC(=NH)NH_2$]; and
- liquid anion exchangers containing primary amine, secondary amine, tertiary amine or quaternary salt functional groups which may be coated on particulate matrices such as cellulose, styrene-divinylbenzene copolymer or Teflon,

for controlling the symptoms of disorders selected from the group consisting of hereditary motor and sensory neuropathies,

giant axonal neuropathy, diabetic polyneuropathy and metabolic symptomology related thereto, Alzheimer's presenile dementia, Alzheimer's senile dementia, Down's syndrome, Pick's disease, Parkinson's disease, amyotrophic lateral sclerosis, and disorders clinically related thereto, Huntington's disease, tinnitus, spinal muscular atrophy, age-related atrophy of peripheral sensory and motor nerves, age-related atrophy of autonomic nerves including symptoms of hypoperistalisis of the alimentary tract, hiatal hernia (partial food regurgitation), urinary incontinence, breathing insufficiency due to diaphragm weakness and decreased autonomic sexual function, age-related atrophy of neurons of the central nervous system, age-onset pathophysiologically related changes in the cardiovascular system, kidney, optic lens and skin, including age-related skin wrinkling, Friedreich's ataxia, alcoholic polyneuropathy, multiple sclerosis, ceroid lipofuscinosis, muscular dystrophy disorders and atherosclerosis.

In a preferred embodiment the non-absorbable polyamine agent or non-absorbable polyamine-related agent or quaternary ammonium salt derivative thereof is used in a dosage in the range of 600 mg/day to 50 grams/day.

In a preferred embodiment, the use of the agent is used orally.

In another aspect of this invention, the invention relates to the use a non-absorbable polyamine chemical agent as defined above for controlling the symptoms of animal disorders selected from a group consisting of:

hereditary motor and sensory neuropathies, giant axonal neuropathy, diabetic polyneuropathy and metabolic symptomology related thereto, amyotrophic lateral sclerosis, and disorders clinically related thereto, tinnitus, spinal muscular atrophy, age-related atrophy of peripheral sensory and motor nerves, age-related atrophy of autonomic nerves including symptoms of hypoperistalisis of the alimentary tract, hiatal hernia (partial food regurgitation), urinary incontinence, breathing insufficiency due to diaphragm weakness and decreased autonomic sexual function, age-related atrophy of neurons of the central nervous system, age-onset pathophysiologically related changes in the

cardiovascular system, kidney, optic lens and skin, muscular dystrophy disorders and atherosclerosis.

In another aspect of the invention, the invention relates to the use of an agent to effectively compete with and covalently bind to disease-induced carbonyl-containing aliphatic or aromatic hydrocarbons for use in the treatment of symptoms of disorders based on neurological disease characterized by the deterioration of intracellular structures and by the spurious pathological chemical crosslinking of intracellular structures, wherein the deterioration and the crosslinking results from reaction of nerve cells and intracellular structures with disease-induced carbonyl-containing aliphatic or aromatic hydrocarbons, wherein the chemical crosslinking comprises covalent-bond crosslinking of the intracellular structures.

In such a preferred embodiment of the use of the present invention, the covalent bond crosslinking of the intracellular structures additionally comprises a neuropathological structure(s) selected from the group consisting of:

a. polymerized aggregates of structural protein filaments such as excess neurofilament accumulation;

b. heterogeneous protein aggregates such as neurofibrillary tangles;

c. amorphous protein and lipid aggregates, such as senile plaques; and

d. lipofuscin granules.

In a preferred embodiment of this aspect of the invention, the use of the agent characterized as a water soluble, small molecular weight chemical having at least one primary amine group or amine-related group thereon is for reaction with carbonyl groups to yield covalently bonded products, and wherein the low molecular weight agent is selected from the group as defined above.

In a preferred embodiment, the use of such an agent is characterized in that the agent does not interact with the normal cell metabolism or does so in a non-cytotoxic manner, is capable of being tolerated in dosages in the range of 600 mg/day to 40 grams/day for extended periods of time and wherein the agent is readily absorbed by the kidney tissue and excreted in

the urine without nephrotoxic consequences. In a preferred embodiment, the invention relates to a use of an agent which comprises a non-absorbable polyamine agent or polyamine-related agent as set forth above. In another preferred embodiment, the use additionally comprises use of a co-agent selected from the group consisting of antioxidants, hormones, suspending reagents, vitamins, metabolites at risk of depletion, sulfhydryl agents and chemical conjugating agents. In another preferred embodiment, the use additionally comprises the use of a co-agent selected from the group consisting of antioxidants, hormones, suspending reagents, vitamins, metabolites at risk of depletion, sulfhydryl agents and chemical conjugating agents.

In another aspect of the invention, the invention relates to a pharmaceutical composition for use in the treatment of the symptoms of disorders selected from the group consisting of:

hereditary motor and sensory neuropathies, giant axonal neuropathy, diabetic polyneuropathy and metabolic symptomology related thereto, Alzheimer's presenile dementia, Alzheimer's senile dementia, Down's syndrome, Pick's disease, Parkinson's disease, amyotrophic lateral sclerosis, and disorders clinically related thereto, Huntington's disease, tinnitus, spinal muscular atrophy, age-related atrophy of peripheral sensory and motor nerves, age-related atrophy of autonomic nerves including symptoms of hypoperistalisis of the alimentary tract, hiatal hernia (partial food regurgitation), urinary incontinence, breathing insufficiency due to diaphragm weakness and decreased autonomic sexual function, age-related atrophy of neurons of the central nervous system, age-onset pathophysiologically related changes in the cardiovascular system, kidney, optic lens and skin, including age-related skin wrinkling, Friedreich's ataxia, alcoholic polyneuropathy, multiple sclerosis, ceroid lipofuscinosis, muscular dystrophy disorders and atherosclerosis,

the composition comprising one or more water soluble, low molecular weight substances selected from:

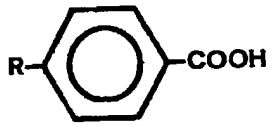
free acid forms, salts, benzene ring isomers, amide derivatives, carboxylic acid ester derivatives and sulfonic acid ester derivatives of the group consisting of:

a. para-aminobenzoic acid (PABA);

b. para-aminomethylbenzoic acid and analogous derivatives of the formula $H_2N-(CH_2)_n-C_6H_4-COOH$ where n = 2-30, including meta- and ortho-benzene ring isomers of the aminoalkyl group and isomers of the aminoalkyl group where the amine is not in the omega position;

c. 4-Amino-3-methylbenzoic acid and other derivatives of PABA or benzene ring isomers thereof wherein such derivatives include from one to four additional ring substituents from the group consisting of methyl group(s), ethyl group(s), or other hydrocarbon group(s) (up to 5 carbons); substituted -OH group(s) of the structure $-OCH_3$, $-C_2H_5$ or higher molecular weight ethers (up to 5 carbons); substituted amine group(s) of the structure -NHR, $-NR_2$ or -NHCOR where R is a hydrocarbon substituent such as $-CH_3$ or derivative thereof (R having 1 to 5 carbons);

d. 4-amidinobenzoic acid, $H_2N-C(=NH)C_6H_4-COOH$, and the following derivatives thereof:



where R= $-NHC(=NH)NH_2$
or $CH_2NHC(=NH)NH_2$
or $(CH_2)_nNHC(=NH)NH_2$
where n = 2 - 10;

e. para-aminophenylacetic acid and analogous derivatives of the formula $H_2N-(CH_2)_n-C_6H_4-CH_2-COOH$ where n = 1-30, as well as methyl and other sidechain hydrocarbon isomers of the aminoalkyl group, and/or hydroxylated derivatives of the sidechain aminoalkyl group, and/or derivatives bearing hydrocarbon or hydroxyl substitutions at the alpha carbon of the acetate group;

f. 4-amidinophenylacetic acid, $H_2N-C(=NH)C_6H_4-CH_2-COOH$;

g. para-aminohippuric acid, $H_2N-C_6H_4-CO-NH-CH_2-COOH$;

h. 3,5-diaminobenzoic acid and other benzene ring diamine isomers;

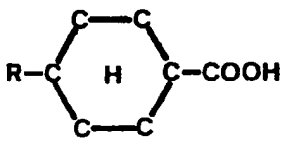
i. 3,5-diaminoalkylbenzoic acid and benzene ring isomers, where aminoalkyl is $H_2N-(CH_2)_n-$ and n = 1 - 30, including hydrocarbon isomers, or where aminoalkyl is $H_2N-(CH_2)_m-CHOH-(CH_2)_n-$ where m = 0 - 15 and n = 0 - 15, including hydrocarbon isomers thereof;

j. para-aminosalicylic acid, and the isomeric amine and hydroxyl derivatives thereof, as well as derivatives wherein the

hydroxyl group has been replaced by a methoxy group or alkyloxy group having 2-10 carbons;

k. 4-amino-2-sulfobenzoic acid, and derivaties thereof including benzene ring isomers and derivatives where the amino group is replaced by an aminoalkyl group having 1-10 carbons, and derivatives where the carboxylic acid group is replaced by a $-(CH_2)_n-COOH$ group (n=1-10);

l. tranexamic acid, 4-(aminomethyl)cyclohexane-carboxylic acid, and the ring positional isomers thereof, and derivatives



wherein R= $-NH_2$

$-(CH_2)_n NH_2$

where n=2-10

$-NHC(=NH)NH_2$

$-CH_2 NHC(=NH)NH_2$

$-(CH_2)_n NHC(=NH)NH_2$

where n = 2 - 10;

m. 6-aminonicotinic acid and the ring isomer derivatives thereof;

n. epsilon-aminocaproic acid, and analogous remaining derivatives of the formula $H_2N-(CH_2)_n-COOH$, where n = 1-30, including isomers wherein the amine is not in the omega position as well as derivatives wherein the alkyl group bears sidechain methyl or other hydrocarbon substitutions and/or hydroxyl group substitutions thereon;

o. 2,3-diaminopropionic acid and analogous derivatives of the formula $(H_3C)_a-CHNH_2-(CH_2)_b-CHNH_2-(CH_2)_c-COOH$ where a = 1 or 0 (in which case omega terminal group is H_2N-CH_2-), b = 0 - 30 and c = 0 - 30, including hydrocarbon isomers of (b) and (c), as well as hydroxylated isomers of (a), (b) and (c);

p. omega-aminoalkylsulfonic acids, $H_2N-(CH_2)_n-SO_3H$ where n = 1 - 20, such as 2-aminoethanesulfonic acid (taurine), including isomeric hydrocarbon derivatives and hydroxy or methoxy derivatives thereof;

q. omega-guanidinoalkylcarboxylic acids, of the general structure $H_2N-C(=NH)NH(CH_2)_n COOH$, where n=1-10;

r. 4-aminobenzenesulfonic acid (sulfanilic acid) and derivatives thereof, including benzene ring isomers such as 2-amino-

benzene-sulfonic acid (or aniline-2-sulfonic acid) and amino-alkylbenzene-sulfonic acids, the aminoalkyl being $H_2N-(CH_2)_n-$, n = 1-15, as well as derivatives having more than one amino- or amino-alkyl- group;

s. sulfanilamide, p-$H_2N-C_6H_4-SO_2NH_2$, including the metabolic precursor derivatives thereof such as 4'-sulfonamido-2,4-diaminoazobenzene hydrochloride and 4'-sulfonamido-2-benzeneazo-7-acetylamino-1-hydroxynaphthalene-3,6-disulfonic acid, and the 1-amino substituted derivatives such as sulfabenz, sulfabenzamide, sulfabromomethazine, sulfacetamide, sulfachlorpyridazine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamoxole, sulfanilamidomethanesulfonic acid, 4-sulfanilamidosalicylic acid, 2-p-sulfanilylanilinoethanol, p-sulfanilylbenzylamine, N^4-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfanitran, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfaquinoxaline, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfazamet, sulfisomidine, sulfisoxazole, and derivatives thereof,

in a dosage rate of from 600 milligrams/day to 40 grams/day, in association with a pharmaceutically acceptable carrier thereof.

In another preferred embodiment, this pharmaceutical composition additionally comprises the use of a co-agent.

In another preferred embodiment, the co-agent used is selected from the group consisting of antioxidants, suspending reagents or the functional equivalents thereto, vitamins, hormones, chemical conjugating agents which facilitate kidney drug elimination, metabolites at risk of depletion or free radical trapping compounds.

In another aspect of this invention, the invention relates to a pharmaceutical composition for use in the treatment of the symptoms of disorders selected from the group consisting of:

hereditary motor and sensory neuropathies, giant axonal

neuropathy, diabetic polyneuropathy and metabolic symptomology related thereto, Alzheimer's presenile dementia, Alzheimer's senile dementia, Down's syndrome, Pick's disease, Parkinson's disease, amyotrophic lateral sclerosis, and disorders clinically related thereto, Huntington's disease, tinnitus, spinal muscular atrophy, age-related atrophy of peripheral sensory and motor nerves, age-related atrophy of autonomic nerves including symptoms of hypoperistalisis of the alimentary tract, hiatal hernia (partial food regurgitation), urinary incontinence, breathing insufficiency due to diaphragm weakness and decreased autonomic sexual function, age-related atrophy of neurons of the central nervous system, age-onset pathophysiologically related changes in the cardiovascular system, kidney, optic lens and skin, including age-related skin wrinkling, Friedreich's ataxia, alcoholic polyneuropathy, multiple sclerosis, ceroid lipofuscinosis, muscular dystrophy disorders and atherosclerosis, the composition comprising one or more non-absorbable polyamine agent or non-absorbable polyamine-related agent or quaternary ammonium salt derivatives thereof selected from the group consisting of:

a. any naturally occurring polysaccharide having beta-1,3, beta-1,4 and/or beta-1,6 linkages containing aminosugars including but not limited to the chitin class of biopolymers having the general structure of **poly-beta-(1→4)-N-acetyl-D-glucosamine** wherein such naturally occurring polysaccharide may be pretreated so as to create a microfibrillated form or microcrystalline form having enhanced surface area, increased water retention capacity and enhanced chemical accessibility such that said pretreated naturally occurring polysaccharides bear at least one free primary amine group and have a high porosity and enhanced susceptibility to chemical reactions;

b. deacetylated naturally occurring polysaccharides, having at least one N-acetylated residue, wherein upon chemical deacetylation thereof, said deacetylated naturally occurring polysaccharide is a high molecular weight derivative bearing primary amine groups directly linked to sugar carbons; including but not limited to chitosan, chondroitin sulfate, hyaluronic acid and keratan sulfate;

c. chemically aminated polysaccharides including but not limited to:

2-amino-2-deoxy-cellulose and other aminodeoxy polysaccharides;

3-aminopropylcellulose;

aminoethylcellulose;

other aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether-, and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates including aminoalkyl derivatives such as

$H_2N-(CH_2)_n-$[carbohydrate] where n = 1 - 30, including alkyl isomers;

amino(hydroxyalkyl)- derivatives such as

$H_2N-(CH_2)_m-CHOH-(CH_2)_n-$[carbohydrate], where m = 0 - 15 and n = 0 - 15;

aminoalkyl-ether- derivatives and amino(hydroxyaklyl)-ether- derivatives such as $H_2N-(CH_2)_n-O-$[carbohydrate] where n = 1 - 30 and $H_2N-(CH_2)_m-CHOH-(CH_2)_n-O-$[carbohydrate] where m = 0 - 15 and n = 0 - 15;

aminobenzyl derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates such as

$H_2N-C_6H_4-(CH_2)_n-$[carbohydrate]

and $H_2N-CH_2-C_6H_4-(CH_2)_n-$[carbohydrate]

and $H_2N-C_6H_4-(CH_2)_n-O-$[carbohydrate] where n = 0 - 30

and $H_2N-C_6H_4-(CH_2)_m-CHOH-(CH_2)_n-O-$[carbohydrate] where m = 0-15 and n = 0-15, including p-, o- and m-benzene ring amino- and aminomethyl- isomers, and alkyl group isomers thereof;

d. primary, secondary and tertiary amine and guanidine derivatives of sucrose polyesters including derivatives having one or more carbonyl trapping functional group wherein the carbonyl trapping functional group is in the omega-, omega-1 or other isomeric position(s) within the fatty acyl chains;

e. synthetic polysaccharides consisting partly or entirely of aminosugars bound by beta-1,3, beta-1,4 and/or beta-1,6 linkages;

f. primary amine containing non-polysaccharide polymers

which are capable of reacting with dietary carbonyl compounds including but not limited to

cholestyramine;

Bio-Rad aminex resin products such as Aminex A-14, Aminex A-25, Aminex A-27 and Aminex A-28 which are quaternary amine derivatives of 8 % crosslinked styrene divinylbenzene copolymer resin;

colestipol;

other anion exchange resins with antihypercholesterolemic properties such as Secholex (also known as polidexide, DEAE-Sephadex or PDX-Cl);

synthetic polymers having o-, m- or p-benzylammonium side chain functional groups;

and structurally related substances such as:

- weakly basic resins prepared by condensation of epichlorohydrin with ethylene imine, primary amines, secondary amines or diamines;
- other epichlorohydrin copolymers with cellulose, chitin or dextran having basic substituent functional groups such as $-OC_2H_4N(C_2H_5)_2$;
- other styrene-divinylbenzene copolymer anion exchange resins having quaternary ammonium functional groups such as $-CH_2N^+(CH_3)_3Cl^-$ or $-CH_2N^+(CH_3)_2CH_2CH_2OHCl^-$;
- styrene-divinylbenzene copolymer anion exchange resins having pyridinium functional groups;
- other styrene-divinylbenzene copolymer anion exchange resins having primary, secondary or tertiary amine functional groups;
- polystyrene resins having guanidine functional groups [e.g., $-NHC(=NH)NH_2$]; and
- liquid anion exchangers containing primary amine, secondary amine, tertiary amine or quaternary salt functional groups which may be coated on particulate matrices such as cellulose, styrene-divinylbenzene copolymer or Teflon, and pharmaceutically active derivatives thereof,

in a dosage rate of from 600 milligrams/day to 50 grams/day, in association with a pharmaceutically acceptable

carrier thereof.

Another aspect of this invention relates to the use of a trapping compound to inhibit rancidity in a food product and extend the shelf life of the food product by trapping and deactivating carbonyl products generated from sugars in the food product, by admixing the food product with the trapping compound, wherein the trapping compound is a small molecular weight amine or amine-related agent selected from the group thereof set forth above.

Another aspect of this invention relates to the use of a trapping compound to inhibit rancidity in a food product and extend the shelf life of the food product by trapping and deactivating carbonyl products generated from sugars in the food product, wherein the carbonyl product which is trapped and deactivated is a Maillard reaction aldehyde precursor or chemically related furan derivative, and wherein the use comprises liquefying the food product, passing the liquified food product through a sieve comprising a non-absorbable polyamine or polyamine-related carbonyl trapping agent selected from the group consisting of non-absorbable carbohydrates, sucrose polyesters and synthetic plastic resins having primary amine groups or derivatives thereof selected from the group set forth above.

In a preferred embodiment, in the use of the present invention, the non-absorbable polyamine or polyamine-related carbonyl trapping agent is selected from a group consisting of those chemical agents and compounds set forth above.

In another aspect of this invention, a trapping compound is used to inhibit rancidity in a food product and extend the shelf life of the food product by trapping and deactivating carbonyl products generated from sugars in the food product in the course of processing the food product, wherein the carbonyl product is a Maillard reaction aldehyde precursor or chemically related furan derivative, the use comprising:

liquefying the food product; mixing the liquified food product for a predetermined time period with a particulate form of one or more non-absorbable polyamine or polyamine-related carbonyl trapping agents selected from the group consisting of non-absorbable carbohydrates, sucrose polyesters and synthetic

plastic resins having primary amine groups or derivatives thereof to form a mixture thereof; centrifuging the mixture for a predetermined time period; and separating the liquid food product from the mixture.

In a preferred embodiment, the use is characterized in that the non-absorbable polyamine or polyamine-related carbonyl trapping agent is selected from a group consisting of the chemical agents and compounds set forth above.

In a preferred embodiment, the use is characterized in that the carbonyl products in the food product are selected from the group consisting of furanaldehydes, and other aldehyde and/or ketone containing compounds, wherein the food products are treated so that they may be regarded as more healthful and promote the health of those consuming the food products and so that the food products may be publicly described as generally furanaldehyde free, aldehyde free or reduced aldehyde.

In another aspect of the invention, the invention relates to the use and pharmaceutical composition of a water soluble, low molecular weight amine substance of molecular weight between 100 and 1,100 selected from the group consisting of those chemical agents and compounds set forth above, for effecting the slowing of skin aging and improving the appearance of skin, by topically using the substance in association with a pharmaceutically acceptable carrier thereof.

II. BACKGROUND OF THE ART: DISEASE-SPECIFIC EVIDENCE OF NEUROFILAMENT ASSOCIATED ETIOLOGY

The prior art sections herein cover information on many diseases which feature neurological damage. This includes both hereditary as well as acquired diseases, as well as neurological damage related to aging.

II(A). Hereditary Motor and Sensory Neuropathies (HMSN, or Charcot-Marie-Tooth Disease) HMSN disorders are a group of peripheral neuropathy syndromes which have been classified into at least seven types (Dyck, PJ, 1984). At least three autosomal dominant forms of HMSN have been defined; chromosome one-linked,

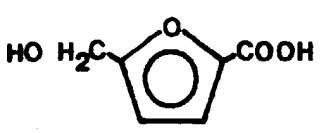
chromosome 17-linked, and non-1/non-17.

In the HMSN II family examined by Goebel and coworkers (1986) peripheral nerve myelinated and, to a lesser extent, unmyelinated axons showed clear evidence of excess neurofilament accumulation, including spheroid (i.e., ballooned) axon segments. Some axons which contained excess neurofilaments did not show any apparent increase in diameter, prompting the investigators to suggest that earlier light microscopy studies may have overlooked this finding. Excess accumulation of neurofilaments, which forces other organelles to the edges of the cytoplasm and creates "balloon" bottlenecks along the axon, may be expected to impede normal axonal transport.

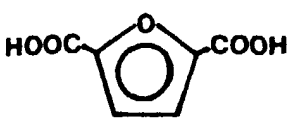
In 1973 Brimijoin and coworkers examined the rate of transport of endogenous dopamine-beta-hydroxylase (DBH) in vitro in samples of normal sural nerve biopsies as well as nerve biopsies from one HMSN I patient, one HMSN II patient and one HMSN III patient. They found that the HMSN proximo-distal slow component transport rates were substantially reduced: 10% of control for HMSN I, 16% for HMSN II and no measurable rate for HMSN III. The investigators concluded that a defect is apparent in the axonal transport system of HMSN nerves. These findings are in accord with the published hypothesis that a spectrum of neurological diseases may share a common basis in being disorders of axonal transport (Tomlinson, DR and Mayer, JH, 1984).

More recently this inventor has published the findings of a study which may provide a molecular basis for the HMSN data noted above (Shapiro, HK et al., 1986; Shapiro, HK and Kahn, GC, 1990). In this study urine samples from five autosomal dominant HMSN I patients (chromosome 17 variety) of the same family and five urine samples from age- and sex-matched normal control subjects were examined. By use of gas chromatography/mass spectrometry the urine concentrations of approximately 150 organic acids could be estimated in each sample. Average HMSN I organic acid values differed most notably from normal values for a set of three physiologically related metabolites, 5-hydroxymethyl-2-

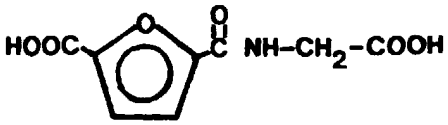
furoic acid, 2,5-furandi-carboxylic acid and 5-carboxy-2-furoyl-glycine. Average patient urine concentrations of these three organic acids were 29%, 50% and 37% of controls, respectively.



5-hydroxymethyl-2-furoic acid



2,5-furandicarboxylic acid

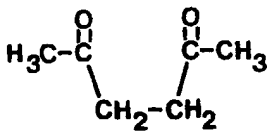


5-carboxy-2-furoylglycine

Previous research studies have determined that 5-hydroxymethyl-2-furoic acid and 2,5-furandicarboxylic acid are oxidation products of an aldehyde precursor, 5-hydroxymethyl-2-furfural (Jellum, E et al., 1973). Decreased levels of furancarboxylic acid excretion suggest that this metabolite, and possibly other aldehyde precursors such as 2,5-furandialdehyde, is not being detoxified and cleared in a normal manner.

5-Hydroxymethyl-2-furfural should be regarded as a potential protein crosslinking agent (Jellum, E et al., 1973, pg. 200). 2,5-Furandialdehyde is even more suspect as a potential crosslinking agent, as it bears two highly reactive aldehyde groups. It is a close structural analogue of 2,5-hexanedione, a potent chemical peripheral neurotoxin implicated in the covalent crosslinking of neurofilaments (structure below). Covalent chemical crosslinking of neurofilaments has been shown to be the basis of 2,5-hexanedione neurotoxicity (Carden, MJ et al., 1986).

2,5-furandialdehyde



2,5-hexanedione

The results of a heretofore unpublished study conducted by this

inventor provide additional evidence that chemical crosslinking of neurofilaments may underlie the etiology of at least some HMSN disorders. In this study the proteins of three HMSN tpye I (chromosome 17 variety) and three control skin fibroblast strains were analyzed by two dimensional gel electrophoresis and subsequent computer image analysis. The HMSN patient skin biopsies came from donors who had previously participated in the organic acid metabolic profiling study noted above. Protein mapping work was carried out at Protein Databases, Inc. (Huntington Station, NY), with financial support provided by the National Foundation for Jewish Genetic Diseases (New York).

In this study 145 protein spots were always seen in each of the three normal fibroblast strains, and 126 corresponding protein spots were always seen in each of the HMSN strains. However, each of the HMSN samples also showed 24 additional protein spots which were never seen in any of the control samples. There were no examples of a protein always seen in each of the control samples but never seen in any of the HMSN samples. The distribution of molecular weights of the additional HMSN-specific protein spots did not correspond to the molecular weight distribution of control protein spots. Rather, it was comparatively shifted up scale. Of the protein spots always seen in control samples, the largest had a molecular weight of 118,000. Of the 24 HMSN-specific protein spots nine had molecular weights in the range of 130,000 to 192,000. The information available from this study can most directly be interpreted as evidence of excess, pathological chemical crosslinking of fibroblast proteins.

There is reason to believe that 5-hydroxymethyl-2-furfural and 2,5-furandialdehyde can originate as by-products of either of two general areas of metabolism, that of sugars and lipids. As discussed in Section VI(B) of this text, these two furanaldehydes form spontaneously from glucose or fructose under mildly acidic aqueous conditions and, as they are readily generated during food cooking, they are part of the human diet. There is reason to believe that these aldehydes, among others, may play a significant role in the etiology of diabetic polyneuropathy

(see Section II[C] of this text). As discussed in Section VI(C) of this disclosure, furanaldehydes may also be generated as secondary products of lipid peroxidation.

II(B). Giant Axon Neuropathy In the case study of Prineas and coworkers (1976) evidence of a generalized abnormality of cytoplasmic microfilament metabolism was found. Peripheral nerves were not generally enlarged, but electron microscopy revealed numerous axonal swellings, or balloon-like structures, randomly positioned along many nerve axons. These axonal spheroids were filled with tightly packed neurofilaments. Both myelinated and unmyelinated fibers were affected.

Prineas and coworkers also noted the presence of discrete masses of cytoplasmic filaments in several other types of cells, including Schwann cells, endoneurial fibroblasts, perineurial cells, endothelial cells of endoneurial capillaries and cultured skin fibroblasts. These non-neuronal cells appeared to otherwise be cytologically normal, including affected Schwann cells. Hence it appears that although many tissues of the body were sub-clinically affected by this microfilament disorder, peripheral nerve axons, which may be a meter in length, are unusually predisposed to suffer the consequences of such filament accumulations.

II(C). Diabetic Polyneuropathy and Related Metabolic Sumptomology This section will concern what is known of the biochemistry of diabetic polyneuropathy and how this pathophysiology appears to serve as a common basis for diabetic complications of other tissues, such as the kidney, the lens, and the vascular system.

Many of the physiological and ultrastructural changes which accompany diabetes are not regarded as phenomena which depend directly on the action of insulin. Rather, they depend on long term hyperglycemia and occur in tissues where glucose uptake is not mediated by insulin. These secondary diabetic phenomena include activation of the polyol pathway and subsequent damage to

eye, kidney and nerve tissue; thickening of capillary basement membranes; and non-enzymatic glycation of a diverse array of proteins, including hemoglobin, lipoproteins, albumin, collagens and other basement membrane proteins (Seifter, S and Englard, S, 1990, pg. 1).

Early diabetic peripheral nerve damage can be documented as slowed nerve conduction velocities. Most diabetic patients will show such decreased conduction velocities, and many have or will eventually show additional signs of nerve damage. Autonomic nerves are also affected in diabetic cases. The nerve hypertrophy seen in diabetic sural nerve samples has been likened to that seen in type I Charcot-Marie-Tooth disease (Johnson, PC, 1985, pg. 334).

Although the specific etiology of diabetic polyneuropathy is still under debate, there is a growing concensus that the axon, not the Schwann cell, is the site of primary etiology (Yamamura, Y et al., 1982, pp. 83-84). Sima (1982) observed that the earliest cytopathological effect seen in sural nerve and spinal ganglion samples from the spontaneously diabetic BB-Wistar rat is the marked disorientation of axonal neurofilaments. Sidenius and Jakobsen (1982) noted the possibility that reductions in slow axonal transport observed in diabetes may result from reduced delivery of neurofilaments to distal axonal segments.

II(C)1. The Polyol Pathway The clinical onset of diabetic polyneuropathy has been positively correlated with increased levels of polyol pathway sugars within peripheral neurons in diabetes mellitus and experimental diabetic models. In addition, use of aldose reductase inhibitors has been shown to reduce intraneuronal levels of sorbitol and fructose, and a concomitant improvement in nerve conduction velocities has been observed. Recognized experimental aldose reductase inhibitors include sorbinil (or CP 45,634, Pfizer), tolrestat (or AY 27,773, Ayerst), statil (or ICI 128,436, I.C.I. Ltd.), ONO 2235 (ONO), M 79,175 (Eisai) and AL 1576 (Alcon) (Kinoshita, JH et al., 1990, pg. 269). Hence convincing evidence has been presented

which indicates that activation of the polyol pathway is a fundamental part of the etiology of diabetic polyneuropathy. Yet the exact sequence of neurotoxic events remains to be defined. Neither sorbitol nor fructose is neurotoxic per se.

Attempts to define how activation of the polyol pathway initiates neuropathy have focused on two concepts; increased intraneuronal osmotic pressure due to sorbitol and fructose accumulation, and possible depletion of intraneuronal myo-inositol, which in turn may limit the activity of Na^+/K^+-ATPase. Yet both of these concepts remain unproven. Ward and coworkers (1972) noted that the observed increases in polyol pathway sugars seen in the streptozotocin rat would not be expected to raise nerve osmotic pressure by more than 5 %. This suggests that osmotic pressure within nerve fibers is not a major etiological factor. Published studies on this question in recent years have failed to clearly define an etiological role for myo-inositol. As Clements (1979) noted, studies on autopsy nerve samples from diabetes mellitus patients showed increased levels glucose, sorbitol and fructose, yet normal levels of myo-inositol. Hale and coworkers (1987) examined sugar levels in nerve biopsies from diabetic and non-diabetic patients undergoing leg amputation. They found elevated levels of glucose, sorbitol and fructose in diabetic samples, yet normal levels of nerve myo-inositol.

Thus although activation of the polyol pathway has clearly been linked to onset of diabetic neuropathy, the mechanism by which this occurs has yet to be determined. As discussed below in Section VI (B), it is the belief of this inventor that conversion of fructose to 5-hydroxymethyl furfural and possibly 2,5-furandialdehyde may in fact be the basis of neurotoxic consequences resulting from activation of the polyol pathway.

II(C)2. Diabetic Non-Enzymatic Protein Glycosylation Studies during the past decade have clearly established that long-term hyperglycemia leads to generalized non-enzymatic addition of

reducing sugar residues to proteins via covalent addition to amine functional groups located on amino acid sidechains. Following initial addition, several structural rearrangements occur which can result in intra- and intermolecular crosslinking of proteins. This is a complex series of non-enzymatic reactions which are not completely defined at this time, yet there is reason to believe that this phenomenon is involved in diabetic vascular changes, cataracts and other secondary diabetic symptomology. Such reactions may also underlie much of the etiology of aging (Pongor, S et al., 1984).

Public domain information on non-enzymatic glycosylation has recently been reviewed (Brownlee, M, 1990). The effects of this phenomenon in long term diabetes are most readily apparent in proteins which have the lowest turnover rates, such as extracellular matrix components. Brownlee and others have made a distinction between early diabetic non-enzymatic glycosylation reactions, which are largely reversible by insulin therapy, and advanced non-enzymatic glycosylation products, which are complexes of long-lived proteins and sugar-derived crosslinking structures. Brownlee (1990, pg. 282) has described evidence that in the diabetic state advanced glycosylation end (AGE) product-modified low density lipoprotein crosslinks with the collagen of vessel walls, which may underlie the accelerated onset of atherosclerosis seen in diabetic patients. The crosslinking of other circulating proteins such as albumin and immunoglobulins to vascular walls has also been observed (Brownlee, M, 1990, pg. 283).

II(D). Alzheimer's Pre-Senile/Senile Dementia and Down's Syndrome Definitive diagnosis of Alzheimer's disease (AD) requires histological analysis of a brain biopsy, with pathological findings including neurofibrillary tangles, senile plaques, as well as granulovascular and Hirano bodies (Cohan, SL, 1989, pp. 164-165). Intracellular neurofibrillary tangles and extracellular senile, or neuritic, plaques are the two principle cytological hallmarks of AD. Such Alzheimer type pathological changes are also characteristic of almost all Down's syndrome cases beyond

thirty years of age (Goodison, KL et al., 1989).

In AD, histological analysis using silver staining reveals thick bundles of fibrillar material dominating the intracellular environment. In AD and most other disorders featuring neurofibrillary tangles ultrastructural studies reveal bundles of paired helical filaments (PHF) of a structure not normally seen. Each PHF is a pair of 10 nm filaments wrapped around one another in 80 nm long intervals. PHF's are also characteristic of Guam Parkinsonism-dementia complex, postencephalitic Parkinsonism, dementia pugilistica and adult stage Down's syndrome, and may be present in other neurological disorders.

As gross intracellular neurofibrillary hyperplasia is much more severe in pre-senile AD, while senile plaques are the most distinctive lesion in senile AD (Wisniewski, HM et al., 1982, pp. 110-112), it appears that aberent neurofibrillary proliferation is a relatively early manifestation of a degenerative process which produces senile plaques as its end stage. The senile plaques of AD characteristically feature distension of neural processes, dendrites in this case. Such axonal and/or dendritic distensions, sometimes described as "balloons," have been shown to be present in several neurological disorders. Their ultrastructure typically reveals excess bundles of neurofibrillary tubules (Wisniewski, HM et al., 1970).

Although the point is still under active investigation, presently available evidence indicates that PHF is derived from protein normally present in nerve cells, as opposed to polypeptides of completely novel origin (Mattson, J and Mattson, MP, 1989; Wisniewski, HM et al., 1982, pg. 116). Immunocytochemical studies have provided evidence for the presence of neurofilament (Elovaara, I et al., 1983; Perry, G et al., 1985; Miller, CC et al., 1986) and neurotubule (Perry, G et al., 1985; Bancher, C et al., 1989) determinants in PHF, as well as determinants for ubiquitin (Bancher, C et al., 1989) and other proteins, some of which may be fortuitously trapped by altered cytoskeleton components (Moran, MA and Gomez-Ramos, P, 1989). Analysis of PHF

by trypsin or chymotrypsin digestion followed by two dimensional peptide mapping has also provided data which indicate the presence of neurofilament and neurotubule proteins (Iqbal, K et al., 1978). Hence the chemical composition of neurofibrillary tangle PHF is known in some detail.

However, the nature of the chemical bonds responsible for holding neurofibrillary tangles together is still poorly understood (Selkoe, DJ, 1982). What limited information is publicly available on this question is compatable with the overall premise of this invention; that cytotoxic consequences result from various forms of spurious covalent bond protein crosslinking, at least some forms of which may be clinically treated by the pharmacological procedures described herein.

The occurrence of excess intraneuronal lipofuscin has also been described as part of the histopathology of AD (Sumpter, PQ et al., 1986). Heart lipofuscin has been shown to have the following general composition: lipids, 20-50%; protein, 30-60%; and strongly pigmented resin-like hydrolysis-resistant material, 9-20%. Although the exact nature of the hydrolysis-resistant chemical bonds remains to be unequivically defined, the similarity between lipofuscin fluorescence and that of Schiff bases formed between malondialdehyde and primary amines suggests that similar chemical crosslinks may be part of lipofuscin structure (Tsuchida, M et al., 1987). Histological and ultrastructural changes analogous to those of AD may also be seen in Pick's disease, another central nervous system disorder of the elderly (Yoshimura, N, 1989).

II(E). Parkinson's Disease (PD) Several clinically related disorders have been described, including postencephalitic parkinsonism, the Parkinsonism-dementia complex of Guam and juvenile parkinsonism. At the microscopic level Parkinson's disease is most characteristically distinguished by the presence of Lewy bodies, each of which is a concentric hyaline cytoplasmic inclusion consisting of protein filaments densely packed in a central core and more loosely packed in an outer zone (Oppen-

heimer, DR, 1976, pp. 612-614). Affected neurons progressively accumulate Lewy bodies and eventually die (Marsden, CD, 1983). Tiller-Borcich and Forno (1988) observed that antibodies to phosphorylated neurofilaments bind to both Lewy bodies of PD and classical Pick bodies, while antibodies to paired helical filaments bind only to Pick bodies. PD dementia patients have also been shown to have cortical neurofibrillary tangles and senile plaques similar to those seen in cases of Alzheimer's disease (Cohan, SL, 1989, pg. 167).

As is the case with Alzheimer's disease neurofibrillary tangles, those of the Guam amyotrophic lateral sclerosis-Parkinsonism dementia complex consist of paired helical filaments (Wisniewski, HM et al., 1982, pg. 112). In a recent immunochemical study by Shankar and colleagues (1989), the neurofibrillary tangles of the Guam amyotrophic lateral sclerosis-Parkinsonism dementia complex were shown to exhibit "robust" immunoreactivity with antibodies for phosphorylated neurofilaments and paired helical filaments of the Alzheimer type, as well as antibodies for the microtubule-associated protein tau. They also noted that "...many axonal spheroids labeled with the antibody to phosphorylated neurofilament, were observed in the loecular layer of fascia dentata and the stratum radiatum and stratum oriens of Ammon's horn." Tan and coworkers (1981) have also noted increased lipofuscin content in cerebral cortex neurons of Guam Parkinsonism-dementia patients.

II(F). Amyotrophic Lateral Sclerosis (ALS) An important clue as to the etiology of ALS was provided by Carpenter in 1968. In examining biopsy material from eleven cases of sporadic ALS he observed the frequent occurrence of large focal axonal spheroids located near nerve perikarya in the spinal cord anterior horns and brainstem motor nuclei. These pathological structures tended to be found in nerve tissues showing relatively early signs of deterioration. Electron microscopic examination showed that these spheroids, or axonal balloons, contained large numbers of neurofilaments. These observations have been confirmed independently (Chou, SM et al., 1970). Some evidence of increased

amounts of neuronal lipofuscin in ALS biopsy material has also appeared (Carpenter, S, 1968; Engel, WK, 1969, pp. 225-227).

III. BACKGROUND OF THE ART: OTHER DISEASES WHICH MAY BE AMELIORATED BY DRUGS WHICH STABILIZE NEUROFILAMENT METABOLISM

As summarized above, studies suggest that diseases discussed in Section II may feature primary etiology which directly involves spurious, pathological crosslinking of proteins. As summarized below, there are other diseases which show evidence of protein-protein and/or protein-lipid crosslinking which may be part of their respective secondary, if not primary, disease etiologies. Patients experiencing these diseases may also benefit from the drug therapy procedures described herein.

III(A). Huntington's Disease (HD) The histopathological study of Tellez-Nagel and coworkers (1974) provides a representative description of HD neuronal cytopathology. Neurons undergoing degeneration demonstrated a variety of intracellular changes which affected lysosomes, Golgi-associated structures, endoplasmic reticulum, mitochondria, chromatin and nuclear membranes. However, they drew particular attention to the progressive appearance of lipofuscin:

> ...One of the most outstanding features was the large and generalized accumulation of lipofuscin in neurons and glial cells...
> ...Large accumulation of lipofuscin granules were frequent in the [nerve cell] perikarya, which sometimes resembled storage cells such as those seen in patients with lipidoses.

II(B). Tinnitus (Nerve Deafness) Like many other clinical catagories described in this text, nerve deafness is actually a syndrome, or, worse yet, a group of syndromes. One part of the nerve deafness complex is Meniere's disease, the symptoms of which include vertigo, tinnitus, and progressive deafness. A number of Meniere's disease clinical sub-varieties have also

been recognized (Ylikoski, J et al., 1980). Another part of the nerve deafness complex includes many patients having Charcot-Marie-Tooth syndrome (HMSN I and II). Autosomal recessive CMT has been described in association with deafness (Cornell, J et al., 1984), as have the X-linked (Cowchock, FS et al., 1985) and autosomal dominant (Kousseff, BG et al., 1982) forms. Nerve deafness has also been described in association with a wide variety of other disorders.

Unfortunately, the histopathological research literature on Meniere's disease and related forms of nerve deafness is sparce. The study by Ylikoski and coworkers (1980) on 40 Meniere's disease vestibular nerve biopsy samples is one of the more thorough investigations on this subject. These samples represented long term clinical deterioration, as they were taken from patients undergoing neurectomy operations to treat intractable vertigo. Electron microscopy revealed disorganization of myelin sheaths, evidence of neuronal loss, and evidence of astrocytic gliosis. Neurons showed large numbers of lipofuscin inclusions and variable quantities of neurofilaments, with some cells showing collections of neurofilaments.

III(C). Spinal Muscular Atrophy At least three clinical subvarieties of this syndrome are recognized; infantile- (Werdnig-Hoffmann disease), juvenile- and adult-onset. The findings of Lee and coworkers (1989) may be cited as a recent and detailed cytopathological study of Werdnig-Hoffmann disease. Their patient showed characteristic atrophy and ballooning degeneration of the spinal cord anterior horn cells, most notably in the lumbosacral segment. Some swollen neurons were also observed in Clarke's column, dorsal root ganglia and the cerebellum. These ballooned neurons were shown to be highly reactive with monoclonal antibody to phosphorylated neurofilament. In Werdnig-Hoffmann disease this ballooning process occurs in the nerve cell perikaryon. Lee and coworkers noted that normally non-phosphorylated neurofilament is predominantly found in nerve cell bodies, with phosphorylation occurring at points in the perikaryon immediately before neurofilament passes

down long axons. They suggested that their findings were in agreement with a previously stated hypothesis that in such patients "...the neurofilaments are abnormally synthesized and phosphorylated in the neuronal perikarya, and/or the axonal transport of phosphorylated neurofilament is impaired, resulting in accumulation in the cell body."

III(D). Age-Related Atrophy of Peripheral Sensory and Motor Nerves, Autonomic Nerves, and Neurons of the Central Nervous System; and Pathophysiologically Related Changes in the Kidney, Optic Lens and Skin Bellamy (1988) offered a definition of aging which is relevant to this text: "...the result of somatic damage arising either internally from errors in the operation of biochemical and physiological systems, or externally from the random impact of physical and chemical factors in the environment." As defined below, these age-related changes share much in common with other disease entities discussed in this invention. At the biochemical level, the two most clearly defined pathological events within mammalian cells appear to be (1) the progressive accumulation of lipofuscin and (2) concomitant appearance of high molecular weight protein aggregates and/or polymeric lipid-protein complexes (Shimasaki, H et al., 1984).

Examination of human sural nerve biopsies has revealed age-related degeneration of both myelinated and non-myelinated fibers. This process includes the occurrence of unusual inclusions within axons consisting of filament bundles which appear more dense than those of normal neurofilaments (Ochoa, J and Mair, WG, 1969). The aging brain takes on a progressively more yellow appearance due to lipofuscin deposition in neurons, glia and other cell types (Calne, DB, 1985, pg. 233). Neuronal loss occurs in many areas of the brain. Senile plaques and intraneuronal neurofibrillary tangles, most notably characteristic of Alzheimer's disease, are also seen with increasing frequency in the normal aging brain (Selkoe, DJ et al., 1982). Neuroaxonal dystrophy, characterized by protein-rich swellings of axons, is also a recognized feature of the aging brain (Calne, DB, 1985, pg. 233; Fujisawa, K, 1967).

As peripheral, autonomic and central nervous system neurons lose functional ability as part of the aging process a variety of body functions under their control are adversely affected. Autonomic nervous system functions include urinary continence, peristaltic movement of the digestive tract, sexual response and breathing. Forms of neurological dysfunction lying within the scope of this invention which may cause urinary incontinence include: Alzheimer's senile dementia, demyelinating diseases (e.g., multiple sclerosis), peripheral nerve lesions, diabetes mellitus and alcoholic neuropathy (Palmer, MH, 1985, pg. 27). Drugs which are presently recognized for use in treatment include cholinergics (e.g., bethanechol), anti-cholinergics (e.g., belladonna) and alpha-adrenergics (e.g., ephedrine) (Palmer, MH, 1985, pg. 58). None of these therapeutic agents have been heretofore recognized as drugs falling within the pharmacological scope of this invention, although this inventor regards the alpha-adrenergics ephedrine, which contains a secondary amine group, and phenylpropanolamine, which contains a primary amine group, as potential carbonyl-trapping agents.

Age-onset changes in kidney cell structure share much in common with diabetic changes. In their study of the aging rat, Bolton and Sturgill (1982) observed time-dependent increases in: number of glomular basement membrane (GBM) irregularities; degree of mesangial sclerosis; mesangial expansion into capillary lumina; number of collapsed capillary loops; degenerative cytoplasmic changes in endothelial, mesangial, visceral, parietal epithelial and tubular cells; proteinuria; interstitial mononuclear infiltrates; and thickness of GBM, Bowman's capsule basement membrane and tubular basement membrane.

Senile pathological changes in the optic lens have been observed which are qualitatively similar to those observed in the diabetic state. As noted by Creighton and coworkers (1978), the process of lens fiber cell death has been ascribed to crosslinking or free radical reactions, or possibly gene mutation. Some chemical evidence is now available which supports these ideas. In their study on human senile and diabetic cataracts, Rao and

Cotlier (1986) noted evidence that crosslinking of lens proteins via nonenzymatic glycosylation appears to be an underlying pathological mechanism for both cataract types. In their analysis of senile cataracts these investigators observed statistically significant decreases in soluble protein content, increases in insoluble proteins, decreases in free epsilon-amino groups of insoluble proteins and increases in observed 5-hydroxymethyl furfural levels (i.e., reducible Maillard products) in insoluble proteins. Similar data were obtained from diabetic cataracts. Earlier studies showed the appearance of covalently crosslinked protein polymers during senile cataract formation (Selkoe, DJ et al., 1982).

Evidence of increased lipid peroxidation in the aged human lens has also been presented. Bhuyan and coworkers (1986) noted that concentrations of lens water soluble, non-protein bound thiobarbituric acid-reactive material remain relatively constant in non-cataractous humans of 11 to 40 years of age, then increase four-fold during 41 to 80 years. This water soluble, carbonyl-containing material includes malondialdehyde as well as substantial amounts of other components not yet identified. These investigators concluded that "...lipid peroxidation of the lens appears to be an age-linked process, enhanced in cataractous lenses."

Changes in skin collagen appear to be a fundamental part of the aging process in this tissue. Long-lived proteins such as collagen, lens crystallins, basement membrane proteins and basic nerve myelin protein have been shown to be more susceptible to non-enzymatic glycosylation (Rao, GN and Cotlier, E, 1986).

Several published studies have presented evidence which implicates lipid peroxidation products in the etiology of atherosclerosis. As summarized by Steinbrecher (1987), there is reason to believe that reactive lipid peroxidation agents form Schiff base adducts with the lysine epsilon-amino groups of low density lipoproteins (LDL). Such modified LDL's are recognized by high-affinity acetyl-LDL receptors located on macrophages,

which results in lipid accumulation. Lipid-laden macrophages appear to be precursors of the foam cells which populate early atherosclerotic lesions (Stein-brecher, UP, 1987).

III(E). Friedreich's Ataxia (FA) Lamarche and coworkers (1982) presented spinal ganglion nerve ultrastructural findings obtained from a typical FA case. These investigators observed variable amounts of lipofuscin granules, with some neurons containing great quantities of this substance. However their most pathonometric finding concerned the presence of neurofilamentous proximal axonal swellings. They noted, in part "...The most striking finding was the presence of numerous axonal swellings usually close to the nerve cell body...The axonal swelling consisted mainly of dense accumulation of neurofilaments measuring about 10 nm...".

III(F). Alcoholic Polyneuropathy Appenzeller and Richardson (1966) conducted a light microscopy study on alcoholic polyneuropathy sympathetic ganglia samples obtained at autopsy. They observed many degenerating giant neurons in sympathetic ganglia. In some sections as many as 30% of the neurons were of the unusually large variety. These cells were filled with a refractile material of eosinophilic, periodic acid-Schiff reaction positive nature which did not stain with scarlet red or Sudan black B. These histological findings indicate that the refractile material was rich in neurofibrils and carbohydrate but had insignificant amounts of lipid. The material, however, was not further characterized. In the same study these investigators reported similar findings in sympathetic ganglia obtained from patients having diabetes mellitus.

III(G). Multiple Sclerosis The results of several published research studies suggest that dysfunctional lipid peroxidation may be a contributing factor in the etiology of multiple sclerosis (Hunter, MI et al.,1985).

III(H). Juvenile Ceroid-Lipofuscinosis Juvenile ceroid-lipofuscinosis cytopathology features prominent accumulation of lipo-

fuscin granules in brain nerve cell bodies. In addition, excess lipofuscin accumulation can readily be demonstrated in many other biopsied tissues, including sural nerve, Schwann cells, lymphocytes, macrophages, skin fibroblasts and smooth muscle cells (Schwendemann, G, 1982).

III(I). Muscular Dystrophy Disorders Several lines of evidence suggest that the secondary etiology of DMD may include disruption of normal lipid peroxidation homeostasis (Hunter, MI and Mohamed, JB, 1986). Kar and Pearson (1979) have presented evidence of increased glutathione reductase and catalase activities in human DMD muscle samples. These investigators also reported increased levels of thiobarbituric acid-reacting substances in DMD muscle, an indication of increased presence of lipid peroxidation aldehyde products such as malondialdehyde. This observation has been independently confirmed (Jackson, MJ et al., 1984).

The accumulation of 100 Angstrom (i.e., 10 nm) protein filaments within axonal processes has been observed in infantile neuroaxonal dystrophy. Similar neurofibrillar abnormalities have been observed in axons of IDPN encephalopathy and vitamin E deficiency, in both axons and perikarya of vincristine neuropathy, and in perikarya of sporadic motor neuron disease (Wisniewski, H et al., 1970, pg. 173).

III(J). Miscellaneous Disorders The clinical neurology literature includes many descriptions of patients having an incipient form of a disease, patients show'ng the recognized symptoms of a disease and additional symptomology, and patients demonstrating concurrent clinical symptomology of two or more recognized disease entities. Such clinical disorders are frequently excluded from biochemical studies due to inherent problems of classification and their happenstance occurrence. Hence comparatively little research information is available on such clinical phenomena. Yet it is the understanding of this inventor that information available on the etiologies of well recognized neurological disorders, as summarized herein, can

also be extrapolated to infer that the drug therapies described in this text may also be applied with success to the incipient and more complex forms of the diseases described above.

IV. BACKGROUND OF THE ART: CHEMICAL MODELS OF NEUROFILAMENT ASSOCIATED NEUROPATHIES

Several experimental models of peripheral neuropathies have been described in some detail in the neuropathology literature. These chemical models have provided important opportunities for investigators to study disease etiologies.

The neurotoxicity of chronic hexane exposure has now been repeatedly confirmed in experimental animal studies (Spencer, PS et al., 1980). In 1973 2-hexanone, a hexane oxidation product, was also shown to be the cause of an industrial outbreak of sensorimotor neuropathy. Subsequent animal studies have established that onset of peripheral neuropathy is most closely related to the maximum endogenous concentration of 2,5-hexanedione (2,5-HD), a metabolite of both n-hexane and 2-hexanone (Spencer, PS et al., 1980). 2,5-Hexanediol, 5-hydroxy-2-hexanone and 2-hexanol have also been shown to be significantly neurotoxic (Krasavage, WJ et al., 1980).

The cytopathological damage observed in hexacarbon neuropathies has much in common with that of giant axonal neuropathy and the morphological changes seen in alloxan diabetic neuropathy (Powell, HC et al., 1978). At the cellular level, hexacarbon neuropathies induce giant axonal swellings which consist of masses of 10 nm neurofilaments. This has been observed in both human samples (Allen, N et al., 1975) and experimental animals such as rats, chickens and cats (Mendell, JR et al., 1974).

Studies on 2,5-hexanedione neuropathy in rats indicate that this hexacarbon or a derivative of it serves as a protein covalent crosslinking agent (Carden, MJ et al., 1986). Current understanding of the etiology of hexacarbon neuropathies is that gamma-diketones such as 2,5-hexanedione preferentially crosslink

the largest neurofilament polypeptide because of its high lysine content. Although the chemical structure(s) of 2,5-hexanedione-lysine derived crosslinks has still not been explicitly defined, in vitro model studies have suggested that one possible mechanism for crosslink formation may be initial formation of dimethylpyrrole, followed by autoxidation to orange chromophore products and concomitant peptide crosslinking (Graham, DG et al., 1982; Boekelheide, K, 1988).

In addition to the findings summarized above, this inventor will note that some evidence exists which suggests that furanaldehydes may play a role in hexacarbon neuropathies. Spencer and coworkers (1980, pg. 310) noted earlier studies on shoe factory workers exposed to commercial hexane which indicated that 2,5-dimethylfuran accounted for 32% of the hexane metabolites found in urine samples. Most of the balance was 2,5-hexanedione (36%) and gamma-valerolactone (30%). Spencer and coworkers (1980, pg. 304) also noted that 2,5-dimethylfuran is a metabolic product of 5-hydroxy-2-hexanone, along with 2,5-hexanedione and gamma-valerolactone.

Williams (1959, pp. 152-153) noted an earlier study by Kuhn and coworkers (1937) which described the metabolic oxidation of 2,5-dimethylfuran to 5-methylfuroic acid. Williams (1959, pp. 545-549) also noted that furfural is converted in vivo to alpha-furoic acid and furylacrylic acid, both of which are recovered in part as their glycine conjugates, and that methylfuran is oxidized to alpha-furoic acid. The formation of furylacrylic acid may be the result of a Perkin synthesis with acetic acid. Williams (1959, pp. 550-551) also mentioned the metabolic conversion of 5-hydroxymethyl furfural, described as a well-known product of the action of acids on hexose sugars, to 5-hydroxymethyl-2-furoic acid. Hence furan derivatives such as 2,5-dimethylfuran may participate in a variety of in vivo progressive oxidation steps.

As the occurrence of genetic peripheral motor and sensory neuropathy has recently been linked to defective furancarboxylic acid

excretion (Shapiro, HK et al., 1986; Shapiro, HK and Kahn, GC, 1990; see Section II [A] of this invention), the prospect that furanaldehydes may play a role in hexacarbon neuropathy may warrent additional consideration.

A variety of additional chemically induced human and/or experimental animal models of peripheral sensorimotor, autonomic and/or central nervous system neuropathies have been described in the public domain biomedical literature (Osuntokun, BO, 1982). As for the hexacarbon neuropathies, published studies of many of these additional chemical models have revealed evidence of pathological protein crosslinking and/or lipofuscin accumulation. These include several well documented animal models of diabetes. Also included in this catagory are peripheral sensorimotor neuropathies induced by vincristine sulfate or vinblastine sulfate (Shelanski, ML and Wisniewski, H, 1969), peripheral sensorimotor neuropathy induced by diamminodichloroplatinum (Kaplan, RS and Wiernik, PH, 1982), doxorubicin peripheral neuropathy (Parhad, IM et al., 1984; Ogura, R, 1982), beta,beta'-iminodiproprionitrile neuropathy (Smith, WT, 1976, pg. 225), progressive neuropathy due to vitamin E deficiency (Diplock, AT, 1984; Wisniewski, H et al., 1970; Lampert, P et al., 1964; Derrick, NM and Wishner, LA, 1967; and Miyagishi, T et al., 1967), acrylamide neuropathy (Gold, BG, 1987; Davenport, JG et al., 1976), tri-orthocresyl phosphate peripheral neuropathy (Prineas, JW, 1969, pg. 582) and carbon disulfide-induced polyneuropathy (Juntunen, J et al., 1974, pg. 363).

V. OBJECTS OF THE INVENTION

Accordingly, it is a general object of this invention to treat neurological diseases and etiologically related symptomology by use of carbonyl trapping agents so as to overcome the disadvantages of the prior art.

V(A). Section II Disorders In particular, it is an object of the present invention that the drug compounds described herein may be of clinical value in treatment of disease symptomology

for disorders featuring well defined neurofilament associated pathology, including: hereditary motor and sensory neuropathies; giant axonal neuropathy; diabetic polyneuropathy and related metabolic symptomology; Alzheimer's presenile/senile dementia; Down's syndrome; Pick's disease; Parkinson's disease; amyotrophic lateral sclerosis; and disorders clinically related to those listed above.

V(B). Section III Disorders It is a further object of the present invention that the drug compounds described herein may be of clinical value in treatment of disease symptomology for neurological disorders featuring axon deterioration as defined in Section III of this invention, including: Huntington's disease; tinnitus (nerve deafness); spinal muscular atrophy; age-related atrophy of peripheral sensory and motor nerves, autonomic nerves, and neurons of the central nervous system as well as pathophysiologically related changes in the cardiovascular system, kidney, optic lens and skin; Friedreich's ataxia; alcoholic polyneuropathy; multiple sclerosis; ceroid lipofuscinosis; muscular dystrophy disorders; and miscellaneous disorders as defined in Section III(J).

V(D). Treatment of Autonomic Disorders It is another object of the present invention that in so far as the therapeutic procedures described herein may be of benefit for improvements in autonomic nervous system function, it is claimed that such procedures may ameliorate symptomology of hypoperistalisis of the alimentary tract; hiatal hernia and partial food regurgitation; urinary incontinence; breathing insufficiency due to diaphram weakness and decreased autonomic sexual function.

V(E). Treatment of Atherosclerosis Symptomology It is yet another object of the present invention that in so far as the therapeutic procedures described herein may serve to covalently bind and sequester agents which may underlie, in part, the etiology of atherosclerosis, it is believed that such procedures may be of benefit in treatment of this disorder.

V(F). Veterinary Applications It is a further object of this invention that the absorbable and non-absorbable amine substances and derivatives thereof described herein may be clinically applied to treat animal disorders comparable to those described in Sections V (A), V (B), V (D) and V (E).

V(G). Tablet Composition In so far as the primary amine and amine-related substances described above may be applied to treatment of the clinical disorders summarized in Sections V (A), V (B), V (C), V (D), V (E) and V (F) of this text, it is claimed that they may be of clinical value when applied under the following conditions.

V(G)1. Absorbable Agent Dosage Absorbable amine agents and amine-related substances are believed to be of value in reducing endogenous concentrations of carbonyl substances when administered orally within a dosage range of 600 mg/day to 40 gm/day.

V(G)2. Non-Absorbable Agent Dosage Non-absorbable amine agents and amine-related substances are believed to be of value in reducing concentrations of carbonyl products present in foods when administered orally within a dosage range of 600 mg/day to 50 gm/day.

V(G)3. Co-Administration of Lipid Peroxidation Inhibitors It is claimed that the therapeutic value of agents described herein may be maximized by administration in conjunction with recognized free radical trapping compounds such as vitamin E (Stuckey, BN, 1968, pp. 214-215) or other agents previously recognized as adjunts which facilitate in vivo capability to inhibit lipid peroxidation, such as selenium (Stuckey, BN, 1968, pg. 236). Citric acid may also be included in this catagory of co-administered agents, as it is recognized as having antioxidant properties (Merck Index, 11th edition, pg. 363). This agent is also recognized as an inhibitor of Maillard reactions (Stuckey, BN, 1968, pg. 210). In a published list of agents which function to supplement the chain-breaking antioxidant property of vitamin E, Tappel (1970, pg. 1138) mentioned ubiquinol,

seleno-amino acids and sulfhydryl compounds (e.g., glutathione, sulfhydryl proteins, cysteine and methionine). Ascorbic acid is not included in this catagory, as published studies indicate that it may function as a pro-oxidant (Ballin, A et al., 1988, pg. 119), may initiate lipid peroxidation (Chojkier, M et al, 1989, pgs. 16957 and 16961), and may readily glycosylate proteins (Slight, SH et al., 1990).

V(G)4. Hormone Co-Administration It is another object of this invention that in so far as the amine agents and amine-related substances described herein may be applied to the treatment of age-onset pathological phenomena, it is believed that the therapeutic value of these products may be maximized by administration in conjunction with human growth hormone and/or other hormones which may be of benefit for the aged patient.

V(G)5. Prophylactic Vitamin Co-Administration It is yet still another object of this invention that the safety and effectiveness of the products described herein may be optimized by co-administration of vitamins which may be inadvertently depleted by the treatment, such as vitamins A, D and K (depleted by cholestyramine use) or vitamin B_6. Pyridoxal, a biologically active metabolite of vitamin B_6, has an aldehyde functional group in its structure.

V(G)6. Co-Administration of Metabolites at Risk of Depletion It is another object of this invention that the safety and effectiveness of the products described herein may be optimized by co-administration of other metabolites, such as glycine or pantothenic acid, which may be depleted within the body during long term drug use.

V(G)7. Co-Administration of Sulfhydryl Agents Noting the well documented ability of carbonyl agents to react with sulfhydryl groups (Jellum, E et al., 1973), it is a further object of this invention that methionine, cysteine, homocysteine and alpha-lipoic acid may also be of clinical benefit as absorbable drugs

capable of covalently binding aldehyde or ketone agents. It is also claimed that these drugs can be used most effectively when administered in conjunction with absorbable and non-absorbable amine and amine-related drugs described herein.

VI(G)8. Factors Affecting Dialy Dosage Schedule It is claimed that a daily protocol of amine and amine-related drug consumption may be defined such that drug products are administered in timed-release and/or color coded tablets or capsules, so as to maximize therapeutic value and facilitate patient compliance.

VI. DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT: DRUG PRODUCTS AND PROPOSED MECHANISM OF PHARMACEUTICAL ACTION OF THE PRESENT INVENTION

VI(A). Introduction The inventive feature disclosed in this text is that absorbable and non-absorbable carbonyl-trapping drugs may be of use in preventing or ameliorating protein and/or lipid crosslinking reactions which appear to underlie the etiology of many neurological diseases and age-related pathological changes. In this section the author summarizes his present understanding of etiological events which have not been publicly recognized up to this point and presents in detail proposed pharmacological procedures for therapeutic intervention, in accordance with the methods of the present invention.

VI(B). Description of the Glucose-Fructose-2,5-Furandicarboxylic Acid Pathway Although not frequently cited for their toxic properties, furan compounds have been identified in a wide variety of food products (Lever, M et al., 1985; Dunlop, AP and Peters, FN, 1953, pgs. 213, 308 and 403; Shimizu, J and Watanabe, M, 1979; Rice, EW, 1972; Baltes, W, 1985; Pettersen, JE and Jellum, E, 1972). Correspondingly, oxidized furan products such as 2,5-furandicarboxylic acid have been identified in normal human urine samples (Williams, RT, 1959, pp. 551-552; Chalmers, RA and Lawson, AM, 1982, pgs. 164 and 180; Lawson, AM et al., 1976, pg. 1286; Pettersen, JE and Jellum, E, 1972; Pinkston, D et al., 1981; Shapiro, HK and Kahn, GC, 1990). The metabolic

origins of 2,5-furandicarboxylic acid are, however, by no means as simple as originally assumed. For example, the metabolic studies of Jellum and coworkers (1973) on two infants clearly established that the dicarboxylic acid is, in fact, generated in vivo from fructose-glucose precursors.

Although few studies have addressed the issue of toxicity of oxidized furans, some published information is available. These reports include toxicity studies on furfural (Konecki, J et al., 1974), 2-furfurol (Dunlop, AP and Peters, FN, 1953, pg. 719) and 5-hydroxymethyl furfural (Ulbricht, RJ et al., 1984). Beyond inferences to be derived from the findings of this inventor, contained herein, it appears that no one has raised questions regarding the possible toxicity of 2,5-funandialdehyde.

By analogy to one of the proposed reactions of 2,5-hexanedione with amino groups of proteins (Graham, DG and Abou-Donia, MB, 1980, pg. 628), one may envision the di-Schiff base protein crosslink formed from a 5-hydroxymethyl furfural or 2,5-furandialdehyde precursor to have the following structure:

VI(B)1. Non-Enzymatic Formation and Reactions of Furans The chemical formation of furans from hexose or pentose sugars is a well recognized reaction which has been applied on an industrial scale for several decades (Dunlop, AP and Peters, FN, 1953, pg. 738). The mechanism of this class of reactions, starting with one of several pentoses or hexoses and ending with furfural or 5-hydroxymethyl furfural, respectively, appears to involve three consecutive dehydration steps (Dunlop, AP and Peters, FN, 1953, pp. 289-290). The ease with which this reaction proceeds is such that the presence of acid is not even required (Dunlop, AP and Peters, FN, 1953, pgs. 281 and 293; Scallet, BL and Gardner, JH, 1945). Murty and coworkers (1977) reported that freshly prepared 10% fructose solution contained 0.2 µg 5-hydroxy-

methyl furfural per ml, while a commercially available 10% fructose intravenous feeding solution contained 4.2 µg/ml.

Jellum and coworkers (1973) demonstrated that commercially prepared mixed fructose/glucose solutions used for intravenous feeding may contain as much as 1.2 gm 5-hydroxymethyl furfural per liter if autoclaved at pH 2.0. By use of gas chromatography/mass spectrometry they also demonstrated the in vivo oxidation of 5-hydroxymethyl furfural to 5-hydroxymethyl-2-furoic acid and 2,5-furandicarboxylic acid in two human newborns. Referring to the furans which were not excreted in the babies' urine, Jellum and coworkers noted that

> The remaining part of the [5-hydroxymethyl furfural] aldehyde and [all of] the 2-(2'-hydroxyacetyl)-furan are probably bound to thiol and amino groups of proteins and enzymes. The furan derivatives present in sterile fructose-containing solutions may consequently cause harmful effects when infused intravenously in humans.

The tendency of fructose to generate furanaldehyde products more readily than glucose is directly based on the chemical nature of the sugars (Dunlop, AP and Peters, FN, 1953, pp. 405-406; Murty, BS et al., 1977).

VI(B)2. Reactive Carbonyl Species as Possible Initiators of Disease Etiology Much of the above discussion has focused explicitly or implicitly on reactions involving covalent addition of aldehydes to side chain amino groups of proteins or amino groups of phospholipids. As summarized in Sections II and III herein, there are reasons to believe that pathological, covalently crosslinked complexes of proteins and/or amine-containing lipids constitute part of the etiological processes which underlie a number of human neurological diseases. Yet in many disorders such intracellular and extracellular ultrastructural complexes may be secondary etiological phenomena, each being the

consequence of some earlier pathological event.

In addition, there are reasons to believe that reactive aldehyde or ketone compounds may on occassion be involved in the primary etiology of a disease. There are at least two particular physiochemical mechanisms by which this might occur. The reactive carbonyl specie(s) may preferentially bind to one or more proteins having enzymatic activity. Alternatively, the reactive carbonyl specie(s) may preferentially bind to a structural protein, or class of structural proteins. These two possibilities may be envisioned in somewhat more specific terms, as discussed below.

In his discussion of age-related changes in the activities of microsomal mixed function oxidase (MFOS) drug metabolizing enzymes, Schmucker (1985) noted data which

> ...support the concept that 'altered' enzyme molecules characterized by reduced catalytic activity, altered heat inactivation profile, unchanged antigenic cross-reactivity, and essentially unchanged kinetic properties constitute a portion of the microsomal NADPH cytochrome c (P-450) reductase pool in the livers of old rats.

Although Schmucker did not address the chemical basis of such changes in enzymatic activities, the work of Davidson and Flynn (1979) could serve to offer one possible explanation. These investigators studied the high-K_m isoform of NADPH-dependent aldehyde reductase of pig kidney. A physiologically similar enzyme, the low-K_m adlehyde reductase of mammalian brain, is one and the same as, or a close biochemical isoform of, the aldose reductase of the polyol pathway (Flynn, TG, 1982). Davidson and Flynn have shown that the high-K_m isoform of this enzyme includes two essential amino acid residues which contain side chain amino groups, one arginine and one lysine. Both of these

key residues appear to be at or near the binding site for NADPH. The investigators demonstrated that the aldehyde reductase is inactivated by 2,3-butanedione, phenylglyoxal, methylglyoxal or 1,2-cyclohexanedione. 2,3-Butanedione was shown to preferentially bind one arginine residue per protein molecule. Hence, although the enzyme is biologically active in catalyzing the conversion of many carbonyl-containing substrates (including phenylglyoxal and methylglyoxal) to corresponding alcohols, some carbonyl-containing species can actually bind at or near the enzyme cofactor binding site so as to inactivate it. Aldose reductase and carbonyl reductase, the two other members of this class of enzymes, have also been examined for the presence of an essential arginine residue. Such a peptide residue is present in the carbonyl reductase, but not in the aldose reductase (Bohren, KM et al., 1987).

This inventor recognizes the possibility that one or more sugar-derived furanaldehyde compounds may actually be involved in the primary, as well as the secondary, etiology of diabetes. Put another way, the primary etiology of human diabetes may involve chronically increased amounts of furanaldehydes from a high sugar diet leading to inactivation of the high K_m aldehyde reductase and/or the carbonyl reductase, with sparing of the aldose reductase. Activation of the polyol pathway, involving aldose reductase, would then only serve to make matters worse.

Interference with the normal activity, or role, of a structural protein might also be a primary etiological event. The normal process of beta cell insulin granule release has been reported to depend on the microtubular system (Pipeleers, DG et al., 1976), which has tubulin as its major protein component. As methylglyoxal and several other aldehydes have been shown to actively bind tubulin (Dianzani, MU, 1978, pg. 253), some in vivo form of such protein binding may be an early diabetogenic event. Dianzani reported, for example, that in vitro colchicine binding to tubulin was inhibited 93.4% by 10 mM methylglyoxal. This certainly raises a question as to the ability of sugar-

derived furanaldehydes to bind to tubulin, an issue which has not yet been investigated. Aldehyde binding to beta cell tubulin may initiate a diabetogenic sequence featuring decreased insulin secretion; elevated levels of blood and tissue glucose; consequent increases in furanaldehydes; activation of the polyol pathway; increased protein crosslinking and onset of secondary diabetic symptomology, including accelerated demise of pancreatic beta cells.

As regards this scenerio, the reader is reminded that (1) mild hyperglycemia and diabetic cataracts develop in the degu, a South American rodent, when captured wild animals are simply maintained on ordinary laboratory rat chow (Varma, SD et al., 1977); (2) experimental diabetic symptomology such as glomerulosclerosis and retinopathy can be induced by high sugar, especially high fructose, diets in the absence of diabetogenic agents such as alloxan (Boot-Handford, RP and Heath, H, 1981); and (3) normal adult humans accustomed to diets low in mono/disaccharide sugars (Yemani immigrants to Isreal) can be inadvertently induced into a diabetic state merely by switching to diets having sugar levels found commonly in the western world (Rosenbaum, E et al., 1971).

VI(B)3. Summary of Inventor's Understanding of Polyol Pathway

Currently the relationship between activation of the polyol pathway and onset of secondary diabetic symptomology is well established in both man and experimental animal models (Flynn, TG, 1982). Yet glucose, sorbitol and fructose are not chemically toxic per se.

It is the preliminary conclusion and understanding of this inventor, not previously recognized by other investigators, that the toxic consequences of polyol pathway activation are the result of increased production of 5-hydroxymethyl furfural and 2,5-furandialdehyde brought on by the initial shift to excess endogenous levels of fructose. As fructose does not readily diffuse out of the tissues prone to secondary diabetic symptomology, the effect would be to generate excess levels of furanal-

dehydes at these sites. It appears that in the uncontrolled diabetic state, and to a lesser extent in the controlled diabetic state, that hyperglycemic endogenous generation of furanaldehydes exceeds the body's capacity to either reduce these products to alcohols (which themselves may be toxic) via aldehyde/ketone reductases or oxidize them to carboxylic acids via aldehyde dehydrogenases.

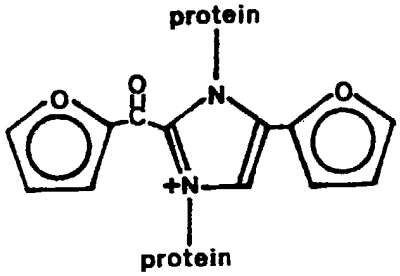
Food chemists confirmed long ago that in Maillard reaction systems, also known as non-enzymatic glycosylation of primary amines, that Amadori products rearrange to form Schiff base-bound 5-hydroxymethyl furfural, and this in turn exchanges with free 5-hydroxymethyl furfural (Keeney, M and Bassette, R, 1959). This is not an isolated observation. Model Maillard reaction studies on difructose-glycine have also demonstrated the generation of free 5-hydroxymethyl furfural (Gottschalk, A, 1972). Mevissen and Baltes (1983) used gas chromatography/mass spectrometry to analzye volatile products generated by the Maillard-type reaction of glucose with phenylalanine. Thirteen of the 29 identified volatile products were furan derivatives, including 2,5-furandialdehyde, 5-hydroxymethyl furfural and 2-furaldehyde. When we compare these empirical observations to the non-enzymatic glycosylation scheme of Brownlee (1990, pg. 281) we see that recognition of furan formation has simply been deleted, a conceptual oversight common in recent studies on the relationship of non-enzymatic glycosylation to diabetes.

A re-evaluation of some of the recently reported data on advanced glycosylation end products may now be offered. In his recent review on this subject Brownlee (1990) did not specifically describe the metabolic origin of the crosslink illustrated below. He suggested that it might originate by an as yet undefined conjugation process involving two Amadori groups and two protein amine groups. This inventor notes the possibility of an alternative metabolic origin. In their paper on the human metabolic origins of furancarboxylic acids Jellum and coworkers (1973) reported detection of 2-(2'-hydroxyacetyl)-furan (see below) in parenteral feeding solutions autoclaved at pH 2.0, as

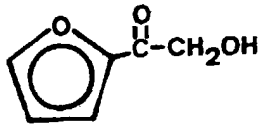
well as 5-hydroxymethyl-2-furfural, levulinic acid and 2-keto-3-deoxyglucose. Jellum and coworkers noted that

> It should be borne in mind that aldehydes in general are reactive compounds capable of interacting with thiol and amino groups of proteins. Because of these properties aldehydes may block SH groups essential for cell division, and thus act as cytotoxic agents. Keto-aldehydes are even more reactive mitotic inhibitors. In this connection particular attention should be paid to the keto alcohol 2-(2'-hydroxyacetyl)-furan which according to our results may be present in fructose-containing solutions. This keto alcohol will undoubtedly be oxidised in the human body to the corresponding keto aldehyde which immediately will interact with thiol groups of the cells, and thus possibly cause unwanted effects. It is interesting to note that not even a trace of unchanged 2-(2'-hydroxyacetyl)-furan or any of its likely metabolites could be detected in the urine of the patients. This indicates that the compound had been completely retained in their bodies.

It seems apparent to this inventor that a condensation process involving two molecules of 2-(2'-hydroxyacetyl)-furan and two protein amino groups may also be a metabolic basis of the AGE product crosslink illustrated by Brownlee (1990).



proposed heterocyclic imidazole derivative crosslink resembling 2-furoyl-4(5)-(2-furanyl)1-H-imidazole



2-(2'-hydroxyacetyl)-furan

In addition to publicly available information, some unpublished findings of this inventor lend further credence to the conclusion that sugar-derived furanaldehydes play a role in the etiology of diabetes. As part of the urine organic acid metabolic screening study on Charcot-Marie-Tooth syndrome patients conducted by this inventor (Shapiro, HK and Kahn, GC, 1990) a urine sample from a recently diagnosed adult onset diabetes patient was also examined. At time of sampling the male patient was 59 years of age and undergoing periodic blood testing subsequent to a coronary bypass operation conducted six months earlier. Starting at four months after the operation the patient began showing excess levels of blood sugar and failed a glucose tolerance test. He was advised of his newly acquired status as a diabetic patient, informed as to how dietary sugar comsumption should be limited henceforth, instructed in the use of a paper indicator product for monitoring urine glucose levels, but not pharmacologically treated for his diabetes prior to urine sampling for the metabolic screening study. The patient was put on daily insulin therapy approximately two years later, yet diabetic complications including confirmed peripheral nerve deficit continued to develop. The patient died of diabetic complications eight years after urine sampling for the metabolic screening study. Levels of urine furancarboxylic acids observed in five normal adult donors for this study and the one newly diagnosed diabetic patient are summarized below. It can be seen from these data that the diabetic patient showed an apparent urine concentration of 5-hydroxymethyl-2-furoic acid which was

urine donors	5-hydroxymethyl-2-furoic acid*	2,5-furandicarboxylic acid*	5-carboxy-2-furoylglycine*
control-1	2.31	23.18	3.56
-2	0.76	21.22	3.97
-3	0.75	11.22	1.71
-4	0.00	1.76	0.51
-5	0.99	23.17	3.49
diabetic	24.08	113.87	17.89

*measured as percent area relative to internal standard

approximately 25 times the concentrations observed for normal donors, while his observed levels of 2,5-furandicarboxylic acid or its mono-glycine derivative were approximately six to eight times higher than corresponding control values.

These observations cannot be explained based on present publicly defined understanding of polyol pathway metabolism or formation of non-enzymatically initiated protein glycosylation reactions. Rather, these findings suggest that this diabetic patient was forming excess in vivo concentrations of furanaldehyde precursors, at least some of which were oxidized and excreted in his urine.

VI(C). Description of Lipid Peroxidation-2,5-Furandicarboxylic Acid Pathway The thought that products of lipid peroxidation might include metabolites such as 5-hydroxymethyl-furanaldehyde and 2,5-furandialdehyde has attracted little, if any, attention within the biomedical research community up to this point. As will be described below, 2,5-dimethyl-furan appears to be a key intermediate in this pathway.

VI(C)1. An Overview of Lipid Peroxidation Kikugawa and Beppu (1987) have summarized present knowledge of lipid biological peroxidation, including the generation of carbonyl compounds and furans. They also noted that lipid radicals, hydroperoxides and their secondary products react with neighboring protein molecules, damaging protein structure and function. Such damage includes formation of fluorescent chromophores, lipid-protein adducts, and protein-protein crosslinks. Using SDS-polyacrylamide gel electrophoresis, these investigators demonstrated that malonaldehyde (also known as malondialdehyde), a bifunctional molecule having two aldehyde groups, can covalently crosslink proteins. This reaction primarily involves Schiff base formation with protein epsilon-amino groups on the sidechains of lysine residues. It is now understood that the proposed role of malondialdehyde as the primary aldehyde product of lipid peroxidation has been overstated by many investigators (Vaca, CE et al., 1988; Halliwell, B, 1984).

Gutteridge and Stocks (1976) noted that the formation of lipofuscin-type fluorescent pigments, which normally occurs slowly with aging, can be induced prematurely in experimental animals by oxygen, pro-oxidant reagents such as iron, or exposure to X-rays. The conceptual similarities between lipid peroxidation-induced protein crosslinking and protein crosslinking associated with non-enzymatic glycosylation has been noted in the research literature (Kikugawa, K and Beppu, M, 1987).

As acetaldehyde is a product of ethanol metabolism, its ability to crosslink proteins may in part underlie the etiology of alcoholic polyneuropathy, presumably by facilitating the spurious crosslinking of lysine-rich neurofilaments. Acetaldehyde has been shown to induce intermolecular crosslinking of polylysine via fluorescent complexes having an excitation maximum at 340-360 nm and an emission maximum at 410-430 nm (Kikugawa, K and Beppu, M, 1987). As large amounts of lipid are normally associated with neurofilaments (Iqbal, K et al., 1978), any physiological anomaly which might increase peroxidation in this microenvironment would predispose for neurofilament crosslinking by reactive carbonyl species.

The generation of water soluble, carbonyl-containing products of lipid peroxidation can be readily demonstrated under simple in vitro conditions (Schauenstein, E, 1967; Esterbauer, H et al., 1982). One group of recognized aldehyde-containing peroxidation products includes agents such as 4-hydroxy-2,3-trans-nonenal, which contains a reactive R-CH=CH-CHO structure (Benedetti, A et al., 1980). In vitro reaction of 4-hydroxy-?,3-trans-nonenal with phosphatidyl-ethanolamine or phosphatidylserine produces fluorescent chromolipids with an excitation maximum of 360 nm and an emission maximum of 430 nm (Esterbauer, H et al., 1986). This corresponds to the fluorescent characteristics of peroxidized microsomal lipids, which show maximal excitation at 350-360 nm and maximal emission at 430 nm. Yet much of the biochemistry of aldehydes generated from lipid peroxidation remains unknown. Benedetti and coworkers (1982) have noted, for example, "...it can nevertheless be concluded that 4-hydroxynonen-

al represents only a small portion of the total amount of aldehydes and other products derived from the peroxidative breakdown of phospholipid-bound arachidonic acid."

Some evidence has been presented which suggests that a slow, age-dependent deterioration of biological systems which counteract lipid peroxidation may be a fundamental part of the aging process (Harman, D, 1971). This concept is sometimes referred to as the free radical theory of aging.

VI(C)2. Generation of 2,5-Dimethyl Furan by Lipid Peroxidation

A variety of furans, aldehydes and ketones have been identified in normal human urine (Zlatkis, A and Liebich, HM, 1971; Matsumoto, KE et al., 1973). These include 2,5-dimethyl furan, 2-methyl furan, other alkyl furans, and a variety of five- to eight-carbon alkyl aldehydes and ketones.

Some of the more definitive work on the relationship between furan metabolism and lipid peroxidation has been reported by Yancey and coworkers (1986). These investigators induced lipid peroxidation in rats by use of a defined diet deficient in both vitamin E and selenium. The onset of an elevated state of in vivo lipid peroxidation was monitored by assay of red blood cell 2-thiobarbituric acid-reactive substances and assay of red blood cell glutathione peroxidase, a selenium-dependent enzyme. TBA-reactive substances increased and glutathione peroxidase activity decreased with onset of an elevated lipid peroxidation state. Capillary gas chromatographic analysis of volatile urine components identified six metabolites which were significantly increased in the vitamin E/selenium deficient animals, as shown below.

Urine samples in this study were also analyzed by trapping aldehydes and ketones with dinitrophenylhydrazine and subsequent high performance liquid chromatography. The results showed that urine of vitamin E deficient animals contained 16 carbonyl compounds which were present at elevated levels of statistical significance. The greatest increases observed were for hydroxy-

Peak areas for those volatile metabolites with significant changes in concentrations due to lipid peroxodation

name	control	lipid peroxidation	lipid peroxidation % of control
2,5-dimethylfuran	202±143	888±356	440
hexanal	1701±137	2784±281	164
2,4-pentadienal	N.D.*	355±13	N.D.*
2-pentylfuran	966±218	1843±756	191
2-furylmethanol	2914±158	6700±901	230
2-decenal	510±193	728±144	143

*N.D. = not detected in control

[data reproduced from Yancey, M et al., 1986, pg. 53]

acetylaldehyde (676%), benzaldehyde (538%) and furfural (487%). In discussing their findings, Yancey and coworkers concluded, in part:

> Both capillary GC and LC results appear to implicate aldehydes (both normal and unsaturated) and related compounds, furan derivatives, as characteristic products of lipid peroxidation. Elevated aldehyde levels were also noticed in our earlier investigations of urinary metabolites of both long-term diabetic rats and genetically diabetic mice. Since an increased lipid peroxidation process has been associated with the diabetic condition, it is not surprising that known peroxidation metabolites should be more abundant in diabetic than normal urine samples...
> Increased lipid peroxidation clearly results in a greater production of metabolites that are either proven or suspected neurotoxins.

VI(C)3. Evidence of In Vivo Oxidation of 2,5-Dimethyl-Furan

Williams (1959, pp. 550-551) also described two particular examples of in vivo furan oxidation reactions which have been demonstrated in mammals, the oxidation of 2,5-dimethyl-furan to 5-methyl-2-furoic acid and the oxidation of 5-hydroxymethyl-

furfural to 5-hydroxymethyl-2-furoic acid. In principle, the process of enzymatically converting hydrocarbon functional groups such as a methyl group of 2,5-dimethyl-furan to a carboxylic acid group involves three consecutive oxidation reactions. In vitro omega oxidation of heptane by rat liver microsomes, an example of a step 1 reaction, has been shown to produce several isomeric alcohols (Frommer, U et al., 1972). Step 2 in this process may be mediated by mammalian alcohol dehydrogenases (ADH), which catalyze the reversible oxidation of alcohols into aldehydes using NAD as a cofactor (McFarland, JT and Chu, Y, 1975). Kassam and coworkers (1989, pg. 569) noted earlier studies which demonstrated that mammalian liver ADH's show broad substrate specificity and reported that human class I beta-1 ADH oxidizes furfuryl alcohol at approximately the same rate as ethanol.

Several mammalian aldehyde dehydrogenases have been described which have wide substrate specificities. One or more of these enzymes may be capable of catalyzing the last step in this proposed metabolic pathway, the oxidation of furanaldehydes to furancarboxylic acids. The broad specificity mammalian microsomal aldehyde dehydrogenase has been shown to oxidize aromatic substrates such as benzaldehyde as well as aliphatic substrates (Antonenkov, VD et al., 1987).

As summarized above, 2,5-dimethyl-furan is a recognized secondary product of lipid peroxidation and there is reason to believe that it may be oxidized in vivo to products such as 5-hydroxymethyl-2-furancarboxylic acid and 2,5-furandicarboxylic acid. This, in turn, suggests that 5-hydroxymethyl furfural and 2,5-furandialdehyde may be metabolic intermediates in this process.

One report, heretofore unexplained, may represent a demonstration of the existence of the entire metabolic pathway, starting with fatty acid peroxidation and ending with recovered furancarboxylic acids. In their report on the furancarboxylic acids of human urine Mrochek and Rainey (1972) described two cases. Apart from the study presented by this inventor and

coworkers on Charcot-Marie-Tooth peripheral neuropathy (Shapiro, HK et al., 1986; Shapiro, HK and Kahn, GC, 1990), these appear to be the only two examples of pathological furancarboxylic acid metabolism reported as of now in the medical literature. In their discussion of the apparent metabolic relationship of 2,5-furandicarboxylic acid, 5-hydroxymethyl-2-furoic acid, 5-hydroxymethyl-2-furoylglycine and 2-furoylglycine, Mrochek and Rainey (1972) described studies on two cancer patients.

Noting earlier work by Flaschentrager and coworkers, Mrochek and Rainey (1972) proposed that perhaps all four of these furan derivatives are products of uronic acid metabolism. Yet the inability of Pettersen and Jellum (1972) to reproduce Flaschentrager's in vivo galacturonic acid study leaves the observations of Mrochek and Rainey apparently without basis. An alternative understanding of the findings of Mrochek and Rainey is proposed herein. The exposure of living organisms to high energy radiation is a well recognized mechanism for initiating in vivo lipid peroxidation (Ayene, SI and Srivastava, PN, 1989; Rejholcova, M and Wilhelm, J, 1989: Siems, W et al., 1990). The description of the two cancer patients noted above is brief. Yet this inventor surmises that both patients may have been undergoing periodic radiation treatment. One administration of radiation therapy for patient B was noted by Mrochek and Rainey, yet presumably this was not the first such treatment. Patient A, for example, was noted to be resistant to chemotherapeutic treatment. If these patients were undergoing regularly scheduled sessions of radiation therapy, then it is conceivable that lipid peroxidation and excretion of furancarboxylic acids may have been fluctuating according to radiation exposure. The summary of events offered by Mrochek and Rainey suggests to this inventor that they fortuitously sampled their patients at times of high lipid peroxidation and high furancarboxylic acid excretion, when the metabolic consequences of their most recent treatments were still in effect. When one patient was sampled again eight days after radiation exposure and found to be excreting normal levels of furancarboxylic acids, post-radiation lipid peroxidation was apparently minimal. This inventor sur-

mises that the occurrence of high energy radiation exposure, a known inducer of lipid peroxidation, and supranormal excretion of furancarboxylic acids is not merely coincidental. Alternatively, one or both of the cancer patients noted above may have been receiving Adriamycin, a commonly used anti-tumor agent known for its ability to induce lipid peroxidation (Ogura, R, 1982).

It is the unique belief and understanding of this inventor that the long term generation of furanaldehyde agents as by-products of lipid peroxidation can serve as a metabolic basis or underlying contributing factor in the etiology of diabetic symptomology, the etiology of other neurological diseases featuring evidence of Schiff base type chemical crosslinking phenomena, and in the etiology of age-related symptomology.

It seems reasonable to this inventor that the hereditary motor and sensory neuropathy patients previously discussed are experiencing toxic long term consequences of furanaldehyde exposure as a consequence of defective ability to oxidize furanaldehydes which are normal products of lipid metabolism. Failure to dispose of these reactive metabolites efficiently may predispose the patients to pathological events initiated by spurious protein crosslinking.

VI(D). Proposed Mechanism for In Vivo Trapping of 5-Hydroxymethyl-Furanaldehyde, 2,5-Furandialdehyde and Other Carbonyl-Containing Metabolites: Absorbable Pharmacological Agents For the most part, the pharmacological reactions of the present invention are based on the ability of primary amine compounds to react with aldehyde functional groups of potentially toxic agents, yielding covalently bound Schiff base products. Several examples of chemically analogous reactions, presented within other contexts, have been publicly presented. Representative examples are discussed below. These model chemical systems are directly analogous to the proposed mechanism of drug action which is the basis of the present invention.

In considering the specific details of the proposed drug therap-

ies described herein, one of the key practical questions which arises early on is to define the normal tissue concentration of thiobartituric acid-reacting aldehydic substances in mammalian tissue. In a section of the forum discussion at the end of Dianzani's 1978 paper T. F. Slater addressed the question of endogenous levels of aldehydes. In his laboratory he observed levels of thiobarbituric acid-reactive substances in normal rat liver in the range of 0.5 µmol/l to 1 µmol/l.

A secondary beneficial aspect of the drug therapies disclosed herein may be the conservation of thiamine, or vitamin B-1. Any disease state which generates excess aldehyde metabolites may predispose for the reaction of such metabolites with the primary amino group of thiamine, effectively lowering the endogenous level of the vitamin. For similar reasons, the drug therapies disclosed herein may effect conservation of vitamin B-12 (cyanocobalamin), which has six primary amine groups (Merck Index, 11th ed, pg. 1577).

One form of application of this invention would be the prophylactic use of such procedures by healthy adult individuals in order to prevent possible onset of neurogenic diseases, and various complications thereof, such as those described above. On such a basis, this invention, or parts thereof, may be applied on an indefinite basis.

Another form of application of this invention would be its use as a medical treatment protocol for treatment of patients having diseases such as those described in sections II and III herein. As applied to a patient having a neurological disease, the intended effect of the method of treatment of this invention would be to qualitatively decrease the endogenous concentration of one or more neurotoxic aldehyde or ketone agent. This, in turn, would permit normal, slow regenerative processes to occur. As such, published studies regarding industrial exposure of humans to 2-hexanone (Allen, N et al., 1975) or acrylamide (Davenport, JG et al., 1976) provide information on patient recovery following removal from exposure to toxic agents of the

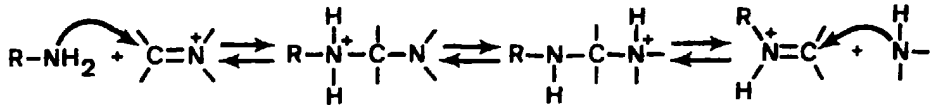
kind which interfere with neurofilament metabolism, indicating that endogenous regenerative processes require between six and twelve months subsequent to removal of toxin from the environment before qualitative improvement in clinical status may be observed. Thus, by analogy, use of the method of this invention to treat patients having chronic neurodegenerative diseases may also require a minimum of six to twelve months of ongoing use before one may expect to observe improvement in clinical status.

VI(D)1. Chemical Model Systems of Proposed Drug Action Comments by Feeney and coworkers (1975, pg. 141) provide an appropriate introduction to this subject:

> A wide variety of substances with $-NH_2$ groups condense with carbonyl compounds...This condensation of primary amines with aldehydes and ketones to give imines was first discovered by Schiff (1900). The overall equilibrium greatly favors hydrolysis in aqueous solution for aliphatic aldehydes. With aromatic aldehydes, the equilibrium is shifted in favor of Schiff base formation. It is important to note that increasing the nucleophilic strength of the amine will increase the rate of the carbonyl-amine reaction but will have almost no effect on the position of the equilibrium.

These comments suggest that the amine-containing carbonyl-trapping drugs described herein should have particular promise for binding furanaldehydes, which are aromatic. These comments also suggest that doses of absorbable amine drugs may require in vivo concentrations in the range of 1:100 to 1:1,000 (carbonyl: amine) in order to achieve clinical effectiveness. This, in turn, suggests that therapeutic dosages may lie in the range of grams per day and that only drugs of particularly low toxicity will have human applications. Feeney and coworkers (1975, pg. 144) also noted the phenomenon of Schiff base transimination,

which occurs to a significant extent at neutral pH:



The existence of such non-enzymatic reversible transimination reactions is important within the context of this invention, as it suggests that in vivo both bound and free carbonyl agents may be sequestered by amine-containing drugs.

(a) The direct in vitro addition of p-aminobenzoic acid or ethyl p-aminobenzoate to malondialdehyde or its tautomer, beta-hydroxyacrolein, has been described (Sawicki, E et al., 1963).

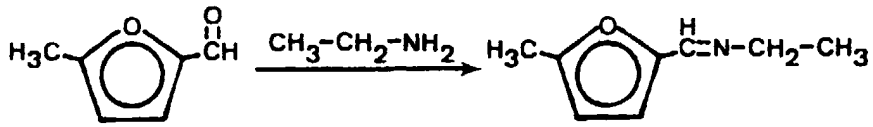
(b) The direct in vitro addition of n-hexylamine to beta-hydroxyacrolein to produce an N,N'-disubstituted 1-amino-3-iminopropene derivative has been reported (Chio, KS and Tappel, AL, 1969). The reaction may be represented as follows:

I — enamine — N,N'-disubstituted-1-amino-3-iminopropene

where I = beta-hydroxyacrolein

R = $-(CH_2)_5-CH_3$

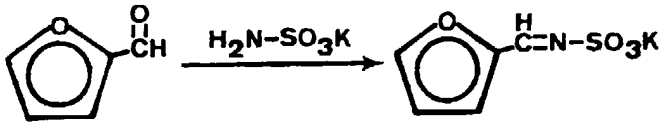
(c) The direct chemical addition of amines to 5-methyl-2-furfural has been described (Holdren, RF and Hixon, RM, 1946). A wide variety of aliphatic and aromatic primary amines can add to furfural in this manner, yielding Shiff base products (Dunlop, AP and Peters, FN, 1953, pg. 353).



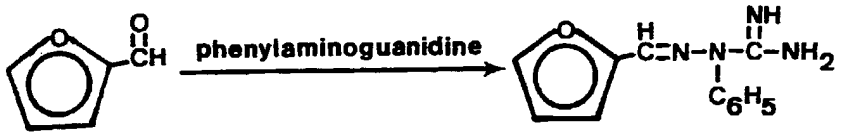
It is proposed that the small molecular weight, absorbable, primary amine drugs and amine-related drugs described herein

will have analogous behavior in vivo, as well as additional characteristics which will facilitate disposal as urine metabolites. Most of these drugs, for example, contain a carboxylic acid group to facilitate uptake and processing by the kidneys.

(d) As described by Dunlop and Peters (1953, pg. 373) earlier work demonstrated the ability of furfural to react with amino-sulfonic salts to produce furfurylideneaminosulfonates:



(e) The reaction of phenylaminoguanidine with furfural (Dunlop, AP and Peters, FN, 1953, pg. 371) may serve as an example of covalent furanaldehyde trapping with a hydrazine.



(f) Urea has been demonstrated capable of binding aldehyde compounds such as furfural (Dunlop, AP and Peters, FN, 1953, pg. 376).

(g) 5-Hydroxymethyl furfural has also been shown to directly react in vitro with two moles of urea to give a diureide (Dunlop, AP and Peters, FN, 1953, pp. 410-411).

VI(D)2. Examples of Absorbable Drug Products Useful in the Present Invention For any amino organic acid agent listed herein as useful in the treatment according to the present invention, it is believed that the salt forms, free acid form, ester derivatives and amide derivatives thereof will also be useful in the claimed invention, as well as other amino organic acid chemical derivatives as specified herein.

(a) Example: Para-aminobenzoic acid (PABA) [150-13-0], including its benzene ring isomers as well as benzene ring hydroxymethyl-, methoxy-, alkyl- (1-10 carbon) substituted and hydroxyalkyl

substituted derivatives. PABA is recognized as being a member of the B vitamin complex (Smith, WT, 1976, pg. 194; Winitz, M et al., 1970, pp. 527-528; Scott, CC and Robbins, EB, 1942), although the biochemical basis of its vitamin-like properties has not been defined. The ability of the human body to clear, i.e., excrete, metabolites of orally administered PABA is quite high (Weizman, Z et al., 1985). Recognized human urine metabolites of PABA, present in addition to the unmodified free acid, include 4-acetylaminobenzoic acid, 4-aminohippuric acid and 4-acetylaminohippuric acid (Young, DS et al., 1971), as well as p-aminobenzoic acid glucuronide (Howie, MB and Bourke, E, 1979).

Besides having vitamin-like properties and being cleared quickly by humans, PABA has also been shown to be an unusually safe drug. When screened for mutagenicity in the Ames Salmonella test, PABA was found to be non-mutagenic (Walsh, DB and Claxton, LD, 1987, pg. 62). When screened in the Ames Salmonella test in the presence of N-methyl-N'-nitro-N-nitrosoguanidine, a proven mutagen, PABA demonstrated an anti-mutagenic effect (Gichner, T et al., 1987). An analogous anti-mutagenic effect of PABA was demonstrated in experiments based on use of hairless mice exposed to ultraviolet light and a chemical carcinogen (Snyder, DS and May, M, 1975).

Several drug products containing PABA have been marketed for human use in the United States. However, it is believed that none have been proposed as effective for the treatments claimed herein. Potassium p-aminobenzoate has been marketed as POTABA (R) in the pure form as an antifibrotic, i.e., skin softening, agent (Drug Information for the Health Care Professional, 8th ed., 1988, pgs. 111-113). As such it has been recognized for treatment of Peyronie's disease; diffuse systemic sclerosis; morphea and linear scleroderma; and dermatomyositis. For such purposes, POTABA (R) is taken orally in average doses of 12 grams/day for up to two years, although human use of 15 - 20 grams/day is recognized. As an ingredient in analgesic tablets, PABA has been marketed for domestic human use (300 mg/tablet) in PABIRIN (R) buffered tablets (with aspirin), in PABALATE (R)

tablets (with sodium salicylate) and in PABALATE-SF (R) tablets (with potassium salicylate), as described in Physicians' Desk Reference, 34th ed., 1980, pgs. 849 (with aspirin) and 1430 (with salicylates). Five percent PABA in a cream base has also been marketed as a sunscreen product (Physicians' Desk Reference, 34th ed., 1980, pg. 849).

As with the molecular basis of PABA's vitamin-like properties, the basis of its presently recognized therapeutic action has not been explicitly defined. In its summary on systemic use of PABA the Drug Information for the Health Care Professional text (8th ed., 1988, pg. 111) presented the following statement (reproduced herein its entirety):

> Mechanism of action: The mechanism by which aminobenzoate potassium exerts its antifibrotic effect is not known. It has been postulated that fibrosis results from an imbalance of serotonin and monoamine oxidase (MAO) mechanisms at the tissue level. Fibrosis is believed to occur when an excessive serotonin effect is sustained over a period of time. This could be the result of too much serotonin or too little MAO activity. Aminobenzoate potassium increases oxygen utilization at the tissue level. It has been suggested that this increased oxygen utilization could enhance the degradation of serotonin by enhancing MAO activity or other activities that decrease the tissue concentration of serotonin.

This inventor sees no relationship of such comments to the subject matter contained herein, in particular to the use of amine drugs in the treatment of neurological diseases. Hence the clinical applications of PABA claimed in this invention are regarded by the inventor as new and novel.

Some evidence has been publicly presented which indicates that amine agents (beta-aminopropionitrile, D-penicillamine and p-aminobenzoic acid) can inhibit the transition of newly synthesized soluble collagen to highly crosslinked insoluble

collagen in hamsters concomitantly treated with bleomycin to induce fibrosis (Zuckerman, JE et al., 1980). In this study on experimental pulmonary fibrosis Zuckerman and coworkers noted that

> PABA has been shown to inhibit the synthesis of glycosaminoglycans in cultured fibroblasts. Adequate tissue concentrations of glycosaminoglycans appear to be necessary for collagen deposition. The antifibrotic action of PABA may, therefore, be the result of direct inhibition of glycosaminoglycan synthesis leading to inhibition of NSI [neutral salt insoluble] collagen accumulation.

This proposed mechanism of action is separate from that claimed for PABA in the present invention, which is use as a covalent chemical sequestering agent for toxic carbonyl substances.

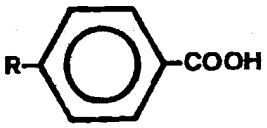
Small molecular weight amines may act as substrates for endo-gamma-glutamine:epsilon-lysine transferases (EC 2.3.2.13), which in theory might interfere with natural peptide crosslinking processes such as fibrin crosslinking and collagen crosslinking. However, in PABA the direct attachment of the amine group to the benzene ring is a structure which serves as a poor substrate for such enzymes (Lorand, L et al., 1979). Lorand and coworkers demonstrated that synthetic amine substrates for these transferase enzymes ideally include a sidearm structure such as $H_2N-(CH_2)_5-X$ which apparently fits in a narrow active site groove. As PABA is a poor synthetic substrate for such enzymes, it apparently plays no role in normal transferase mediated protein crosslinking and its pharmacological mechanism of action has remained heretofore unexplained. What relationship, if any, the studies of Lorand and coworkers (1979) may have to that of Zuckerman and coworkers (1980) remains to be determined. The overall process of collagen crosslinking is complex, involving lysine, hydroxylysine and histidine (Tanzer, ML, 1973), and the interrelationship(s) of PABA to this process remain largely

unknown.

(b) Example: Para-aminomethylbenzoic acid and analogous derivatives of the formula $H_2N-(CH_2)_n-C_6H_4-COOH$ where n = 2-30, including meta- and ortho-benzene ring isomers of the aminoalkyl group and isomers of the aminoalkyl group where the amine is not in the omega position.

(c) Example: 4-Amino-3-methylbenzoic acid and other derivatives of PABA or benzene ring isomers thereof wherein such derivatives include from one to four additional ring substituents from the group comprising methyl group(s), ethyl group(s), or other hydrocarbon group(s) (up to 5 carbons); substituted -OH group(s) of the structure $-OCH_3$, $-C_2H_5$ or higher molecular weight ethers (up to 5 carbons); or substituted amine group(s) of the structure -NHR, $-NR_2$ or -NHCOR where R is a hydrocarbon substituent such as $-CH_3$ or derivative thereof (R having 1 to 5 carbons).

(d) Example: 4-Amidinobenzoic acid, $H_2N-C(=NH)C_6H_4-COOH$. Also included in this class are the following derivatives:



where R= $-NHC(=NH)NH_2$
or $CH_2NHC(=NH)NH_2$
or $(CH_2)_nNHC(=NH)NH_2$
where n=2-10

Also included in this class are analogous derivatives wherein the carboxylic acid group is replaced by an acetic acid functional group ($-CH_2-COOH$).

(e) Example: Para-aminophenylacetic acid and analogous derivatives of the formula $H_2N-(CH_2)_n-C_6H_4-CH_2-COOH$ where n = 1-30, as well as methyl and other sidechain hydrocarbon isomers of the aminoalkyl group, and/or hydroxylated derivatives of the sidechain aminoalkyl group, and/or derivatives bearing hydrocarbon or hydroxyl substitutions at the alpha carbon of the acetate group.

(f) Example: 4-Amidinophenylacetic acid, $H_2N-C(=NH)C_6H_4-CH_2-COOH$,

and analogous derivatives [$H_2N-C(=NH)-(CH_2)_n-C_6H_4-CH_2-COOH$ where n = 1-30], including methyl and other sidechain hydrocarbon isomers of the amidinoalkyl group, and/or hydroxylated derivatives of the sidechain amidinoalkyl group, and/or derivatives bearing hydrocarbon or hydroxyl substitutions at the alpha carbon of the acetate group.

(g) Example: Para-aminohippuric acid, $H_2N-C_6H_4-CO-NH-CH_2-COOH$. Also included in this class are analogous derivatives of the formula $H_2N-(CH_2)_n-C_6H_4-CO-NH-CH_2-COOH$ where n=1-30, as well as methyl and other sidechain hydrocarbon isomers of the aminoalkyl group and/or hydroxylated derivatives of the sidechain aminoalkyl group. Also included in this class are the analogous amidinoalkyl hippuric acid derivatives.

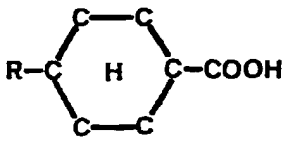
(h) Example: 3,5-diaminobenzoic acid and other benzene ring diamine isomers.

(i) Example: 3,5-diaminoalkylbenzoic acid and benzene ring isomers, where aminoalkyl is $H_2N-(CH_2)_n-$ and n = 1 - 30, including hydrocarbon isomers, or where aminoalkyl is $H_2N-(CH_2)_m-CHOH-(CH_2)_n-$ where m = 0 - 15 and n = 0 - 15, including hydrocarbon isomers.

(j) Example: Para-aminosalicylic acid. Also included in this class are the isomeric amine and hydroxy derivatives, as well as derivatives wherein the hydroxy group has been replaced by a methoxy group or alkyloxy group (2-10 carbons).

(k) Example: 4-Amino-2-sulfobenzoic acid, and structures including benzene ring isomers, derivatives where the amino group is replaced by an aminoalkyl group (1-10 carbons), and derivatives where the carboxylic acid group is replaced by a $-(CH_2)_n-COOH$ group (n=1-10).

(l) Example: Tranexamic acid, or 4-(aminomethyl)cyclohexanecarboxylic acid. Also included in this class are:



where R= $-NH_2$

$-(CH_2)_nNH_2$ where n=2-10

$-NHC(=NH)NH_2$

$-CH_2NHC(=NH)NH_2$

$-(CH_2)_nNHC(=NH)NH_2$ where n=2-10

Ring positional isomers of these structures are also included in this class.

(m) Example: 6-Aminonicotinic acid as well as ring isomer derivatives.

(n) Example: Epsilon-aminocaproic acid [60-32-2] and analogous remaining derivatives of the formula $H_2N-(CH_2)_n-COOH$ where n = 1-30, including isomers wherein the amine is not in the omega position as well as derivatives wherein the alkyl group bears sidechain methyl or other hydrocarbon substitutions and/or hydroxyl group(s) substitutions.

(o) Example: 2,3-Diaminopropionic acid and analogous derivatives of the formula $(H_3C)_a-CHNH_2-(CH_2)_b-CHNH_2-(CH_2)_c-COOH$ where a = 1 or 0 (in which case omega terminal group is H_2N-CH_2-), b = 0 - 30 and c = 0 -30. Hydrocarbon isomers of (b) and (c) are also included in this catagory of drug, as well as hydroxylated isomers of (a), (b) and (c).

(p) Example: Omega-aminoalkylsulfonic acids, $H_2N-(CH_2)_n-SO_3H$ where n=1-20 (Fujii, A et al., 1977), such as 2-aminoethanesulfonic acid (taurine), including isomeric hydrocarbon derivatives and hydroxy or methoxy derivatives thereof.

(q) Example: Omega-guanidinoalkylcarboxylic acids, of the general structure $H_2N-C(=NH)NH(CH_2)_nCOOH$, where n=1-10 (Fujii, A et al., 1977). Also included in this class are derivatives having isomeric structures of the $-(CH2)_n-$ hydrocarbon unit and/or hydroxylated isomers of the $-(CH2)_n-$ hydrocarbon unit.

(r) Example: 4-Aminobenzenesulfonic acid (sulfanilic acid) and related chemical structures such as 2-aminobenzenesulfonic acid. Also included in this class are aminoalkyl-benzenesulfonic acids, where the aminoalkyl is $H_2N-(CH_2)_n-$, n = 1-15, as well as derivatives having more than one amino- or amino-alkyl-group, such as 2,5-diaminobenzenesulfonic acid.

(s) Example: Sulfanilamide, $p-H_2N-C_6H_4-SO_2NH_2$. Also included in this class are metabolic precursor derivatives such as 4'-sulfonamido-2,4-diaminoazobenzene hydrochloride and 4'-sulfonamido-2-benzeneazo-7-acetylamino-1-hydroxynaphthalene-3,6-disulfonic acid (Williams, RT, 1959, pp. 485-486). This class also includes the 1-amino substituted derivatives such as sulfabenz, sulfabenzamide, sulfabromomethazine, sulfacetamide, sulfachlorpyridazine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamoxole, sulfanilamidomethane-sulfonic acid, 4-sulfanilamidosalicylic acid, 2-p-sulfanilylanilinoethanol, p-sulfanilylbenzylamine, N^4-sulfanilylsulfanil-amide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfanitran, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfaquinoxaline, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfazamet, sulfisomidine, sulfisoxazole, and related structures (Merck Index, 11th ed., pp. 1403-1414).

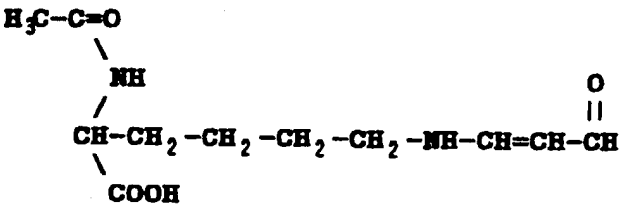
VI(E). Proposed Mechanism for In Vivo Trapping of 5-Hydroxymethyl Furanaldehyde, 2,5-Furandialdehyde and Other Carbonyl-Containing Metabolites: Non-Absorbable Pharmacological Agents

As described in preceeding sections, the diet is a significant source of carbonyl agents. These agents may be contributing factors in the aging process, may predispose humans for other neurodegenerative disorders, may be contributing factors in atherosclerosis, may be contributing factors in inflammatory diseases and may also be contributing factors in the initiation

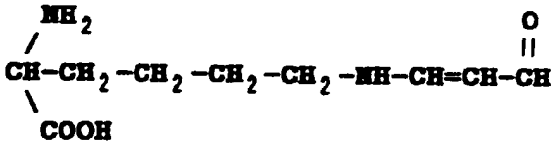
of carcinogenesis. Such carbonyl agents, while contributing positively in some instances to the flavor of foods or beverages (e.g., cheeses or wines), have no recognized nutritional value. It is proposed herein that dietary supplements such as those defined below can be of public health benefit by their ability to covalently trap dietary aldehydes and ketones. The agents described in this section can accomplish this function because they bear primary amine groups or derivatives thereof. As large molecular weight molecules which are non-digestible they have the capacity to pass through the digestive tract, acting in effect as another form of dietary fiber. These non-absorbable polyamine trapping substances may be divided into three classes; naturally occurring polyamine polysaccharides, chemical derivatives of naturally occurring polysaccharides, and synthetic polyamine polymers.

VI(E)1. Chemical Model System of Proposed Non-Absorbable Drug Action The fate of malondialdehyde given orally to rats may serve as an example of the metabolism of dietary aldehydes, and how an understanding of this process can be used to define non-absorbable carbonyl-trapping drugs. Studies by Draper and coworkers (1986) demonstrated that the primary form of "bound" MDA in rat or human urine is N-alpha-acetyl-epsilon-(2-propenal)lysine. This is the biologically acetylated derivative of the MDA-lysine adduct N-epsilon-(2-propenal)lysine, as shown on the following page.

Draper and coworkers (1986) were able to generate N-epsilon-(2-propenal)lysine in vitro by exposing beef muscle protein to MDA, followed by treatment with pepsin and hog intestinal juice. This indicates that the epsilon-amino groups of dietary protein lysine residues can covalently bind dietary aldehyde under conditions found in the intestinal tract. As such, chemically analogous primary amine groups on non-absorbable drugs should also be capable of covalently binding dietary aldehydes under conditions to be found in the intestinal tract. In this case, however, the bound carbonyl species would be excreted in the



N-alpha-acetyl-epsilon-(2-propenal)lysine



N-epsilon-(2-propenal)lysine

feces, thus preventing subsequent in vivo exposure to dietary carbonyl agents.

In their study Draper and coworkers noted that N-alpha-acetyl-epsilon-(2-propenal)lysine was found in urine of fasted rats or animals fed on MDA-free diets, indicating that the MDA-lysine adduct also forms in vivo. These investigators referred to earlier work which demonstrated that the MDA concentration normally found in food is in the range of <0.1 to 10 ppm (0.1 to 10 μM), which gives some idea of dietary aldehyde concentrations.

VI(E)2. Examples of Non-Absorbable Drug Products Useful in the Method of the Present Invention VI(E)2(a). Naturally Occurring Amine-Containing Polysaccharides. Any naturally occurring polysaccharide featuring beta-1,3, beta-1,4 and/or beta-1,6 linkages which contains aminosugars may be regarded as a non-digestible, potentially active carbonyl trapping agent. The chitin class of biopolymers may be cited as an example of such an agent, having the general structure of **poly-beta-(1→4)-N-acetyl-D-glucosamine**. A form of microcrystalline chitin has been described in which some of the acetyl groups have been removed, revealing free amine groups (Austin, PR et al., 1981, pg. 750). Chitins obtained from different sources feature different degrees of amine deacetylation (Austin, PR et al., 1981, pg. 752).

VI(E)2(b). Chemical Derivatives of Naturally Occurring Polysaccharides. Various pretreatment procedures may be applied to naturally occurring polysaccharides prior to generation of chemical derivatives. Generation of microcrystalline polysaccharides is one example of such a pretreatment procedure. As applied to cellulose or chitin (Yalpani, M, 1988, pg. 389), this yields a colloidal processed form of polysaccharide featuring high porosity and enhanced susceptibility to chemical reactions. Generation of "microfibrillated" cellulose or chitin is another example of a pretreatment procedure which produces enhanced surface area, increased water retention capacity and enhanced chemical accessibility (Yalpani, M, 1988, pg. 390). Use of strong (> 18%) sodium hydroxide is still another recognized pretreatment, or activation, procedure found to be helpful as a starting point for preparing chemical derivatives of polysaccharides (Yalpani, M, 1988, pg. 214).

VI(E)2(b)(1). Deacetylation of Naturally Occurring Polysaccharides. A variety of polysaccharides have been identified which are rich in N-acetylated residues. Upon chemical deacetylation these carbohydrates yield high molecular weight derivatives bearing primary amine groups directly linked to sugar carbons, i.e., no sidearm spacer units present.

(i) Chitosan. This is the deacylated form of chitin. As described in the Merck Index, 11th edition (pg. 316) chitin is a cellulose-like biopolymer the composition of which consists mostly of N-acetyl-D-glucosamine residues covalvently linked by beta-1,4 bonds. Chemical deacylation removes acetate, generating primary amine groups still covalently bound to the polysaccharide. Chitosan has recognized uses in water treatment, in photographic emulsions, and in improving the dyability of synthetic fabrics and fibers. The free amine groups in this substance give it polycationic and chelating properties (Austin, PR et al., 1981).

(ii) Chondroitin sulfate. This is a mucopolysaccharide found commonly in mammalian tissue. It consists of repeating disac-

charide units, each of which has a D-glucuronic acid residue beta-1,4 linked to an N-acetylchondrosine residue (Merck Index, 11th edition, pg. 344).

(iii) Hyaluronic acid. This mucopolysaccharide is also found commonly in mammalian tissues. It consists of glucuronic acid and glucosamine residues bound by beta-1,3 and beta-1,4 linkages (Merck Index, 11th edition, pp. 751-752).

(iv) Keratan sulfate. This mammalian glycosaminoglycan consists of a repeating disaccharide unit of a C-6 sulfated C-2 N-acetylated sugar residue and a galactose residue linked by beta-1,4 bonds (Yalpani, M, 1988, pp. 27-28).

VI(E)2(b)(2). Chemical Amination of Polysaccharides.

(i) 2-Amino-2-deoxy-cellulose. Cellulose can be aminated by a process of selective oxidation, oximation and subsequent reduction with lithium aluminum hydride (Yalpani, M, 1988, pp. 281-282).

(ii) Alternative amination procedures. Aminodeoxy polysaccharides can also be prepared via azide or hydrazide intermediates or by reductive amination using sodium cyanoborohydride (Yalpani, M, 1988, pg. 281). Besides being applied to cellulose, other non-digestible polysaccharides such as curdlan (Yalpani, M, 1988, pg. 22) may be aminated by such chemical procedures.

(iii) 3-Aminopropylcellulose. Reaction of cyanoethylcellulose with borane-tetrahydrofuran or borane-dimethyl sulfide complexes in tetrahydrofuran generates 3-aminopropylcellulose (Yalpani, M, 1988, pgs. 250 and 255). In this derivative each primary amine group is at the end of a three carbon sidearm.

(iv) Aminoethylcellulose. This chemical has been previously marketed as an anion exchange column chromatography resin (Sigma Chemical Co. catalog, Feb. 1981) and used as such in protein purification studies (Fasold, H, 1975, pp 481-482).

(v) Other aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether-, and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates. Noting that the chemical methodology for producing such derivatives is documented in public domain literature, the biomedical application of such derivatives for therapeutic purposes described herein is also claimed. This would include:

aminoalkyl derivatives $H_2N-(CH_2)_n-$[carbohydrate] where n = 1 - 30, including alkyl isomers

amino(hydroxyalkyl)- derivatives:

$H_2N-(CH_2)_m-CHOH-(CH_2)_n-$[carbohydrate], where m = 0 - 15
n = 0 - 15

aminoalkyl-ether- derivatives and amino(hydroxyaklyl)-ether- derivatives:

$H_2N-(CH_2)_n-O-$[carbohydrate]
where n = 1 - 30

and

$H_2N-(CH_2)_m-CHOH-(CH_2)_n-O-$[carbohydrate]
where m = 0 - 15
n = 0 - 15

(vi) Aminobenzyl- derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates. As the aromatic amine group is far less strong a base than its aliphatic counterpart, this class of non-absorbable amines should be less chemically active than amino- and aminoalkyl- derivatives described above.

$H_2N-C_6H_4-(CH_2)_n-$[carbohydrate]
and $H_2N-CH_2-C_6H_4-(CH_2)_n-$[carbohydrate]
and $H_2N-C_6H_4-(CH_2)_n-O-$[carbohydrate] where n = 0 - 30
and $H_2N-C_6H_4-(CH_2)_m-CHOH-(CH_2)_n-O-$[carbohydrate] where m = 0-15
n = 0-15

This includes p-, o- and m-benzene ring amino- and aminomethyl-

isomers, and alkyl group isomers.

VI(E)2(b)(3). Aminated Sucrose Polyesters. Mixtures of fatty acid hexa-, hepta- and octaesters of sucrose, known as sucrose polyester, are not hydrolyzed by pancreatic lipase enzymes and are not absorbed in the intestine (Jandacek, RJ, 1984). It is proposed and claimed herein that primary, secondary and tertiary amine; amino-guanidine; and guanidine derivatives of sucrose polyesters may be of benefit in reduction of dietary carbonyl substances, analogous to the proposed action of other non-absorbable agents described herein. Such derivatives of sucrose polyesters would include structures in which the carbonyl trapping functional group is in the omega-, omega-1 or other isomeric position(s) within the fatty acyl chains. Such aminated sucrose polyesters may be used in pure form as a dietary supplement, or may be prepared as a coating on a particulate carrier such as cellulose or styrene divinylbenzene copolymer resin.

VI(E)2(c). Synthetic Polyamine Polymers. VI(E)2(c)(1). Synthetic polysaccharides consisting partly or entirely of aminosugars bound by beta-1,3, beta-1,4 and/or beta-1,6 linkages may be regarded as non-absorbable potential carbonyl trapping agents.

VI(E)2(c)(2). Primary amine containing non-polysaccharide polymers. Amine functional groups may be covalently attached to a wide variety of synthetic non-digestible polymers. Like their sugar-based counterparts, these agents should be capable of reacting with dietary carbonyl compounds.

(i) Cholestyramine [11041-12-6]. As described in the Merck Index (11th edition, pg. 342), this agent is "a synthetic, strongly basic anion exchange resin containing quaternary ammonium functional groups which are attached to a styrene-divinylbenzene copolymer. Main constituent: polystyrene trimethylbenzylammonium as Cl- anion, also contains divinylbenzene (ca. 2 %) water (ca. 43 %). Cross linkage %: 1 - 10. Particle size: 50 - 100 mesh." This agent is already marketed for human

use on a prescription basis as an antihyperlipoproteinemic drug by virtue of its ability to non-covalently bind bile salts. This substance is also known as Dowex 1-X2 (Bio-Rad). Similar resins are Dowex 2-X2, and Amberlite IRA-400, 401 and 410 (Rohm and Haas) (Niederwieser, A, 1975, pg. 410).

(ii) Bio-Rad Aminex resins (Bio-Rad Laboratories); products Aminex A-14 (catalog # 147-6106), Aminex A-25 (catalog # 147-6202), Aminex A-27 (catalog # 147-6300) and Aminex A-28 (catalog # 147-6400). These commercially available products are described as quaternary amine derivatives of 8 % crosslinked styrene divinylbenzene copolymer resin (source: "Chromatography, Electrophoresis and Membrane Technology" catalog, April 1975, Bio-Rad Laboratories, pgs. 30-32). Seta and coworkers (1980) described Aminex A-27 as being a microreticular anion-exchange resin of particle size 12 - 15 um.

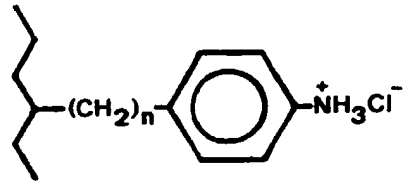
(iii) Colestipol [50925-79-6]. As described in the Merck Index (11th edition, pg. 387), this agent is "a basic anion exchange resin described as a high molecular weight copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane (hydrochloride), with approximately 1 out of 5 amine nitrogens protonated, for which no specific molecular weight information is available, due to the highly crosslinked and insoluble nature of the material." This agent is already marketed as an antihypercholesterolemic agent (Cooper, EE et al., 1977).

(iv) Secholex (R)[67167-34-4], also known as polidexide, DEAE-Sephadex and PDX-C1. This is another anion exchange resin with recognized antihypercholesterolemic properties (Thale, M and Faergeman, O, 1978; Simons, LA and Myant, NB, 1977).

(v) Diaion CDR-10. Seta and coworkers (1980) used three mesh sizes of this high performance liquid chromatography resin (6, 11 and 25 um) to separate organic acids. They described Diaion CDR-10 as a "...strongly basic macroreticular anion-exchange resin...obtained from Mitsubishi (Tokyo, Japan)." They also described the product as being 35% crosslinked. Comparing

Diaion CDR-10 to Aminex A-27, Seta and coworkers described Diaion CDR-10 as having higher crosslinkage, larger porosity and better adsorptivity of organic acids.

(vi) Synthetic polymers having o-, m- or p-benzylammonium side chain functional groups. Such aromatic amine derivatives should be far weaker bases than aliphatic amine groups, such as those of amino-propylcellulose or epsilon-aminocaproic acid (Feeney, RE et al., 1975, pp. 136-137).



n=1-30

The agents claimed in this section also include structurally related substances such as

(a) weakly basic resins prepared by condensation of epi-chlorohydrin with ethylene imine, primary amines, secondary amines or diamines (Walton, HF, 1975, pg. 316)

(b) other epi-chlorohydrin copolymers with cellulose, chitin or dextran having basic substituent functional groups such as $-OC_2H_4N(C_2H_5)_2$ (Walton, HF, 1975, pg. 317)

(c) other styrene-divinylbenzene copolymer anion exchange resins having quaternary ammonium functional groups [e.g., $-CH_2N^+(CH_3)_3Cl^-$ or $-CH_2N^+(CH_3)_2CH_2CH_2OHCl^-$] (Walton, HF, 1975, pg. 318)

(d) styrene-divinylbenzene copolymer anion exchange resins having pyridinium functional groups (Walton, HF, 1975, pg. 318)

(e) other styrene-divinylbenzene copolymer anion exchange resins having primary, secondary or tertiary amine functional groups (Walton, HF, 1975, pg. 318)

(f) polystyrene resins having guanidine functional groups [e.g., $-NHC(=NH)NH_2$] (Walton, HF, 1975, pg. 320), and

(g) liquid anion exchangers containing primary amine, secondary amine, tertiary amine or quaternary salt

functional groups which may be coated on particulate matrices such as cellulose, styrene-divinylbenzene copolymer or Teflon (Blasius, E et al., 1975, pp. 853-856).

VI(F). Prior Pharmacological Studies Certain amine agents have recognized antioxidant properties. These include N,N'-di-(sec-butyl)-p-phenylenediamine (Scott, G, 1965, pg. 120), aniline and aniline N-subsyituted agents (Scott, G, 1965, pg. 125). In the present invention focus is placed on primary amine agents, as such agents are known to covalently react with carbonyl agents to yield Schiff base-type products (Feeney, RE et al., 1975, pg. 141). By contrast, N-substitution with hydrocarbon functional groups tends to increase amine antioxidant activity (Scott, G, 1965, pgs. 125 and 148). These are two distinct chemical phenomena. The antioxidant property of amines depends on their ability to act as electron donors to alkoxy or alkylperoxy radicals (Scott, G, 1965; pgs. 127, 145 and 158). The carbonyl trapping property of amines depends on their ability to form Schiff base-type addition products.

Although the abilities of amines to react with alkylperoxy radicals and carbonyl groups are publicly well recognized, the application of these principles to the clinical treatment of neurological disorders and metabolically allied symptomatic phenomena is not. Within the body of information encompassing previously issued United States patents and biomedical journal publications a wide spectrum of pharmaceuticals have been described as potential therapeutic agents for one or more of the diseases falling within the context of this invention. A comprehensive review of previous public domain information conducted by this inventor has failed to reveal any examples of the claims included herein.

It should be noted that the proposed amine and amine-related therapeutic agents described above in Sections VI(D) and VI(E) have chemical structures which are fundamentally different from those of recently investigated experimental aldose reductase inhibitors. Recognized experimental aldose reductase inhibitors

include sorbinil (or CP 45,634, Pfizer), tolrestat (or AY 27,773, Ayerst), statil (or ICI 128,436, I.C.I. Ltd.), ONO 2235 (ONO), M 79,175 (Eisai) and AL 1576 (Alcon). One or more primary amine functional groups are not present in the chemical structure of any of these experimental drugs (Kinoshita, JH et al., 1990, pg. 269). The structural differences between the proposed amine and amine-related therapeutic agents claimed herein and known experimental aldose reductase inhibitors serve to underscore that these two classes of agents act by different pharmacological mechanisms. The experimental aldose reductase inhibitors are specific enzyme inhibitors. The chemical trapping agents described and claimed in the present invention should act by sequestering toxic carbonyl-containing metabolic or dietary products. Yet each of these drug classes may have therapeutic value in the treatment of secondary symptoms of diabetes.

The work encompassed by several United States patents assigned to Rockefeller University discloses the inhibition of the formation of advanced glycosylation end products of target proteins. In United States patent 4,758,583 ("Method and agents for inhibiting protein aging," Cerami, A et al., 1988) the inventors described

> ...an agent or compound capable of inhibiting the formation of advanced glycosylation end products of target proteins by reacting with the carbonyl moiety of the early glycosylation product of such target proteins formed by their initial glycosylation. Suitable agents may contain an active nitrogen-containing group, such as a hydrazine group, and may further be at least partially derived from amino acids. Particular agents comprise aminoguanidine, alpha-hydrazinohistidine and lysine. The method comprises contacting the target protein with the composition. Both industrial and therapeutic applications for the invention are envisioned, as food spoilage and animal protein aging can be treated.

> ...Accordingly, the compositions useful in the present invention comprise or contain agents capable of reacting with the active carbonyl intermediate of the early glycosylation product. Suitable agents include compounds having an active nitrogen-containing group or substituent such as a hydrazine group. Also, the agent or compound may be at least partially derived from an amino acid, including the esters and amides thereof, as compounds having this derivation are generally biocompatible with the target proteins to be contacted. For example, the agent may comprise a compound selected from the group consisting of aminoguanidine, alpha-hydrazinohistidine and lysine, and possibly mixtures of these agents or compounds. Each of these agents or compounds possesses an active nitrogen-containing substituent that is believed to react with the carbonyl of the early glycosylation product. Consequently, reaction of the agents with the glycosyl-lysine of a protein would prevent this moiety from forming crosslinks with other groups.

The carbonyl-containing early glycosylation products referred to in the quotation noted above are the Amadori products of protein primary amines and various reducing sugars. No other particular compounds beyond those quoted above are claimed in US patent 4,758,583. As stated in the claims section of US patent 4,758,583, the "active nitrogen-containing" agents are hydrazine derivatives, with the exception of lysine. The claims of US patent 4,758,583 are limited to prevention of food spoilage and prevention of animal protein aging by inhibition of formation of protein advanced glycosylation end products. However, in an earlier section of US patent 4,758,583 the inventors state that

> Drug therapy may be used to prevent the increased trapping and crosslinking of proteins that occurs in diabetes and aging which leads to sequelae such as arterial disease, including renal disease, hypertension, retinal damage, and extra-vascularly, damage to tendons, liga-

ments, and other joints. This therapy might retard atherosclerosis and connective tissue changes that occur with diabetes and aging.

It is the understanding of the author of the present invention that the amine compounds and their functional applications claimed herein lie beyond the claims of US patent 4,758,583. By comparison of the text of US patent 4,758,583 to the present text several substantive differences of content and inventor understanding may be noted, as summarized below.

As defined in US patent 4,758,583 the essential chemical agents are hydrazine compounds. No hydrazine compounds are claimed herein for the treatment of age- or diabetes-related etiology, although use of some hydrazine derivatives is disclosed herein regarding treatment of other diseases which feature neurodegenerative changes. The term "active nitrogen-containing group," as mentioned in US patent 4,758,583, is not defined. As such, it may conceivably refer to a diverse spectrum of thousands of nitrogen containing substances, including amino derivatives, nitro derivatives, diazonium salts, nitroso derivatives, heterocyclic bases and possibly other substances. Such a diverse spectrum of substances might include nitrofuran drugs, which are known to induce peripheral neuropathy in humans (Klinghardt, GW, 1967); trinitrotoluene, also known as TNT; or deoxyribonucleic acid, also known as DNA. The inventors of US patent 4,758,583 have not specified the meaning of the term "active nitrogen-containing group" beyond reference to hydrazine derivatives, lysine and lysine derivatives.

US patent 4,758,583 states that "...the agent or compound may be at least partially derived from an amino acid, including the esters and amides thereof...". Yet the term "amino acid" is not defined and lysine is the only example mentioned. By a narrow definition, found commonly in textbooks on chemistry and biochemistry, amino acids are defined as those twenty-six primary and secondary amine carboxylic acid building blocks which constitute the structures of peptides and proteins, which includes

lysine (Morrison, RT and Boyd, RN, 1966, pp. 1098-1101). By the most broad definition, the term "amino acid" might include any chemical having some form of an amine group in its structure together with any form of organic or inorganic acid functional group, which could include carboxylic acid derivatives, phosphoric acid derivatives, sulfonic acid derivatives, or a variety of other acidic functional groups. By this latter definition, thousands of chemical structures might be included.

The inventors of US patent 4,758,583 have not discussed or claimed application of their invention to clinical disorders featuring nerve damage beyond an inferred application to treatment of neurological deficits resulting from diabetes or aging. As such, and distinct from the present invention, they made no statement or inferred comment regarding treatment of other neurological disorders which feature cytopathological accumulations of protein and/or protein/lipid aggregates. Hence US patent 4,758,583 does not disclose the use of pharmaceuticals in treatment of Charcot-Marie-Tooth disorders, giant axon neuropathy, Alzheimer's pre-senile/senile dementia, Down's syndrome, Pick's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, tinnitus, spinal muscular atrophy, Friedreich's ataxia, alcoholic polyneuropathy, multiple sclerosis, ceroid lipofuscinosis, muscular dystrophy disorders and clinically related disorders.

US patent 4,758,583 discloses that the therapeutic agents will prevent protein crosslinking associated with formation of advanced glycosylation end products by reacting with and binding to early glycosylation complexes, the Amadori products. Hence this proposed mechanism of drug action would result in drug agents indefinitely bound to the surfaces of low turnover proteins. Since such drug agents are described in US patent 4,758,583 as binding to the carbonyl group of Amadori products, the otherwise reversible relationship between Amadori product and Schiff base would no longer exist and both drug and sugar residue would remain bound to protein.

It is believed that the absorbable amine-containing and amine-related drugs described herein are weaker bases than the hydrazine derivatives of US patent 4,758,583. Hence, although most of the drugs described herein may have some nominal ability to form addition adducts with Amadori products, this is not understood to be the primary mechanism of pharmacological action. Rather, as defined in Section VI(D)1, it is understood that the absorbable drugs claimed herein will act most readily to combine with aldehyde groups, forming water-soluble complexes. Such drug-aldehyde complexes may then diffuse into the blood, if they do not initially form there, and can then be recognized by kidney tissue and sequestered into urine.

It is believed that the absorbable amine-containing and amine-related agents described herein will act primarily to bind with free aldehyde carbonyl groups such as those of unbound 5-hydroxymethyl furfural, unbound or bound 2,5-furandicarboxaldehyde, or other aldehyde products of lipid peroxidation or other sources. The binding of furanaldehydes to amino groups is recognized as being a reversible process (Keeney, M and Bassette, R, 1959). As discussed by Keeney and Bassette, all of the reactions among Amadori product, sugar Schiff base, unbound sugar, unbound furanaldehyde and bound furanaldehyde Schiff base are recognized as being reversible. This means that at any point a certain fraction of sugar in an amine-reducing sugar non-enzymatic equilibrium system is represented as unbound furanaldehyde. This process of generating non-protein bound, water soluble drug-aldehyde adducts or drug-ketone adducts may be further facilitated by the phenomenon of Schiff base transimination, as outlined in Section VI(D)1 of this present invention.

As described in US patent 4,758,583, the invention would form covalently bonded chemical addition products subsequent to reaction with reducing sugar-amine complexes, thus preventing the formation of advanced glycosylation end products. However, no explanation of the ultimate biochemical fate of such drug-sugar-amine complexes is offered, and presumably such complexes would remain attached to the surfaces of proteins. Yet success-

ful treatment of the neurological sequelae of aging, diabetes and other disorders discussed in Sections II and III herein would require, in most cases, long term or indefinite drug therapy. The simple accumulation of a drug product chemically bound to proteins may be acceptable in in vitro studies and may not overtly affect the results of in vivo animal studies. Yet in order for any such proposed therapeutic agent to have safe practical application to treatment of human symptomology, some forms of effective disposal for both unreacted drug and drug-sugar-amine complexes must exist. No such mechanisms are envisioned in US patent 4,758,583.

By contrast, the absorbable amine-containing and amine-related agents described herein include carboxylic or sulfonic acid functional groups, thus making both unreacted drugs and drug-carbonyl complexes readily recognizable by kidney tissues for active sequestration into urine. While the kidney possesses a high capacity for active removal of many aminated organic acids, the normal amino acids, such as lysine, are an exception to this rule. The kidney has no active process for removing from the blood the normal amino acids which are protein substituents. Hence, the proposed absorbable therapeutic agents mentioned herein have functional groups which predispose them, and presumably their trapped carbonyl derivatives, for effective, efficient removal from the body. However, the "active nitrogen-containing" substances mentioned in US patent 4,758,583 do not.

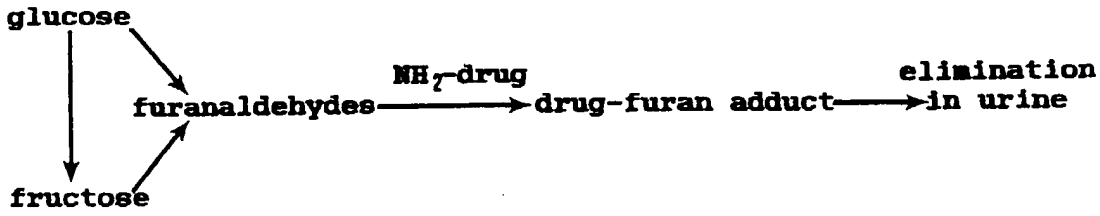
Hence the process of the present invention is not restricted to preventing early protein glycosylation complexes from transforming into advanced glycosylation end products. The present invention would effect the same end, but by a different mechanism. In the present invention water soluble complexes of drug(s) and carbonyl compounds would be formed, permitting outright removal of toxic agents from the body. As it is intended that patients be maintained on such a protocol for months, years or indefinitely, the passage of time would permit diffusion of drug-carbonyl agent complexes out of nerve and other cells and a shift in equilibria of reactions which form Amadori products,

created by removal of protein-bound sugar-derived furan products, which would have the long term effect of limiting protein crosslinking due to advanced glycosylation end products.

US patent 4,758,583 does not describe its invention as a general method of covalently trapping potentially toxic reactive aldehyde and ketone substances which may be generated in vivo or to which a person may be exposed from an environmental source such as food. Rather, they have explicitly stated their understanding that each of their proposed therapeutic agents "...is believed to react with the carbonyl of the early glycosylation product."

By contrast, the present inventor states herein his understanding that the absorbable agents claimed herein may react with a wide spectrum of aldehyde and ketone agents to form covalent adduct products. Such aldehyde and ketone agents may, for example, originate as products of lipid peroxidation, a prospect not envisioned by the inventors of US patent 4,758,583.

As the invention described herein should act to actually remove sugar by-products from the bodies of diabetics as drug-furan complexes, the present invention would serve not merely to limit protein crosslinking but would also serve to create a new mechanism for removing excess sugar. In a simplified form, this process may be envisioned as follows:



The inventors of US patent 4,758,583 do not discuss or claim the possible uses of non-absorbable polymeric amine compounds such as chitosan, cholestyramine or polyaminated cellulose derivatives for either in vivo or in vitro applications.

In US patent 4,900,747 ("Method and agents for removing advanced glycosylation endproducts," Vlassara, H et al., 1990) Dr. Anthony Cerami and his colleagues at Rockefeller University have described an additional invention which addresses the issues of non-enzymatic glycosylation and protein crosslinking, but which is distinct from the invention described herein. In US patent 4,900,747 the inventors described, in part, an invention wherein

> ...a method and associated agents are disclosed for the inhibition and treatment of protein aging in animals by stimulating the bodies of such animals to increase their recognition of and affinity for advanced glycosylation endproducts.
> ...The agents of the present invention comprise one or more stimulator compounds in turn, comprising a natural or synthetic advanced glycosylation endproduct alone or bound to a carrier, said carrier including a material selected from carbohydrates, proteins, synthetic polypeptides, lipids, bio-compatible natural and synthetic resins, antigens, and mixtures thereof. The stimulator compounds could include other advanced glycosylation endproducts that may be prepared from the reaction between sugars and other macromolecules, and monokines which stimulate phagocytic cells to increase their activity toward advanced glycosylation endproducts.
> ...pathologies such as age related or diabetes related hardening of the arteries, skin wrinkling, arterial blockage and diabetic retinal and renal damage are all the result of the excessive build-up or trapping that occurs as the presence of advanced glycosylation endproducts increases. Accordingly, a therapeutic method in accordance with the present invention generally seeking to avert such pathologies contemplates the administration of the agents of the present invention either directly or in suitable pharmacological compositions to stimulate the phagocytic cells to remove advanced glycosylation endproducts from the body with greater speed and efficiency, and to thereby avert the

> onset of the pathologies recited herein.
> ...Thus, the present invention is predicated on the discovery that the phagocytic cells including monocytes and macrophages can be modified by exposure to certain agents or stimulator compounds that potentiate the capability of these cells with respect to their recognition and affinity for, and capability to degrade advanced glycosylation endproducts.

As summarized above, the invention embodied in US patent 4,900,747 describes use of advanced glycosylation end (AGE) products and derivatives thereof as immunostimulating agents so as to increase in vivo capacity for sequestration of AGE product-modified proteins. Hence the invention embodied in US patent 4,900,747 is based upon methodologies which are qualitatively different from those described herein. No in vitro or in vivo use of immunostimulating protocols is envisioned in the present invention.

In US patent 4,908,446 ("Inhibitors of nonenzymatic cross-linking," Ulrich, PC and Cerami, A, 1990) the inventors have elaborated on earlier work as embodied in US patent 4,758,583 to define a class of chemical derivatives of aminoguanidine such that

> Accordingly, the compositions useful in the present invention comprise or contain agents capable of reacting with the active carbonyl intermediate of the early glycosylation product. Suitable agents are the hydrazine derivatives which bear an electron-withdrawing group of the present invention. These agents possess an active nitrogen-containing substituent that is believed to react with the carbonyl of the early glycosylation product.

As described in US patent 4,908,446, chemical analogues of aminoguanidine were screened in vitro for their ability to inhibit glucose mediated crosslinking of bovine serum albumin.

Said agents were also screened in vitro for their capacity to inhibit diamine oxidase, an unwanted effect which may conceivably limit the eventual use of such drugs for treatment of human aging and diabetes symptomology. The invention embodied in US patent 4,908,446 represents a direct extension of claims embodied in US patent 4,758,583 as regards aminoguanidine. As such, the contents of US patent 4,908,446 also lie beyond the claims of the present invention for reasons analogous to those summarized above.

Without further elaboration the foregoing will so fully illustrate my invention that others may, by applying current or future knowledge, adopt the same for use under various conditions of service.

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VII. CLAIMS

I claim:

1. Use of a water soluble, low molecular weight substance containing a primary amine or a primary amine group, for use in the treatment of symptoms of disorders based on neurofilament associated pathology and/or pathophysiologically related symptomology.

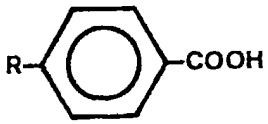
2. Use of a water soluble, low molecular weight substance (100 to 1,100 range of molecular weights) selected from the group consisting of free acid forms, salts, benzene ring isomers, amide derivatives, carboxylic acid ester derivatives and sulfonic acid ester derivatives of the group consisting of:

a. para-aminobenzoic acid (PABA);

b. para-aminomethylbenzoic acid and analogous derivatives of the formula $H_2N-(CH_2)_n-C_6H_4-COOH$ where n = 2-30, including meta- and ortho-benzene ring isomers of the aminoalkyl group and isomers of the aminoalkyl group where the amine is not in the omega position;

c. 4-Amino-3-methylbenzoic acid and other derivatives of PABA or benzene ring isomers thereof wherein such derivatives include from one to four additional ring substituents from the group consisting of methyl group(s), ethyl group(s), or other hydrocarbon group(s) (up to 5 carbons); substituted -OH group(s) of the structure $-OCH_3$, $-C_2H_5$ or higher molecular weight ethers (up to 5 carbons); substituted amine group(s) of the structure $-NHR$, $-NR_2$ or $-NHCOR$ where R is a hydrocarbon substituent such as $-CH_3$ or derivative thereof (R having 1 to 5 carbons);

d. 4-amidinobenzoic acid, $H_2N-C(=NH)C_6H_4-COOH$, and the following derivatives thereof:



where R= $-NHC(=NH)NH_2$
or $CH_2NHC(=NH)NH_2$
or $(CH_2)_nNHC(=NH)NH_2$
where n = 2 - 10;

e. para-aminophenylacetic acid and analogous derivatives of the formula $H_2N-(CH_2)_n-C_6H_4-CH_2-COOH$ where n = 1-30, as well as methyl and other sidechain hydrocarbon isomers of the amino-alkyl group, and/or hydroxylated derivatives of the sidechain

aminoalkyl group, and/or derivatives bearing hydrocarbon or hydroxyl substitutions at the alpha carbon of the acetate group;

f. 4-amidinophenylacetic acid, $H_2N-C(=NH)C_6H_4-CH_2-COOH$;

g. para-aminohippuric acid, $H_2N-C_6H_4-CO-NH-CH_2-COOH$;

h. 3,5-diaminobenzoic acid and other benzene ring diamine isomers;

i. 3,5-diaminoalkylbenzoic acid and benzene ring isomers, where aminoalkyl is $H_2N-(CH_2)_n-$ and n = 1 - 30, including hydrocarbon isomers, or where aminoalkyl is

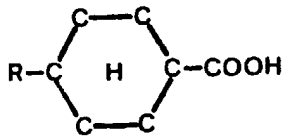
$$H_2N-(CH_2)_m-CHOH-(CH_2)_n- \text{ where } m = 0 - 15 \text{ and } n = 0 - 15$$

including hydrocarbon isomers thereof;

j. para-aminosalicylic acid, and the isomeric amine and hydroxyl derivatives thereof, as well as derivatives wherein the hydroxyl group has been replaced by a methoxy group or alkyloxy group having 2-10 carbons;

k. 4-amino-2-sulfobenzoic acid, and derivatives thereof including benzene ring isomers and derivatives where the amino group is replaced by an aminoalkyl group having 1-10 carbons, and derivatives where the carboxylic acid group is replaced by a $-(CH_2)_n-COOH$ group (n=1-10);

l. tranexamic acid, 4-(aminomethyl)cyclohexane-carboxylic acid, and the ring positional isomers thereof, and derivatives



wherein R= $-NH_2$

$-(CH_2)_nNH_2$ where n=2-10

$-NHC(=NH)NH_2$

$-CH_2NHC(=NH)NH_2$

$-(CH_2)_nNHC(=NH)NH_2$ where n = 2 - 10;

m. 6-aminonicotinic acid and the ring isomer derivatives thereof;

n. epsilon-aminocaproic acid, and analogous remaining derivatives of the formula $H_2N-(CH_2)_n-COOH$, where n = 1-30, including isomers wherein the amine is not in the omega position as well as derivatives wherein the alkyl group bears sidechain methyl or other hydrocarbon substitutions and/or hydroxyl group

substitutions thereon;

o. 2,3-diaminopropionic acid and analogous derivatives of the formula $(H_3C)_a-CHNH_2-(CH_2)_b-CHNH_2-(CH_2)_c-COOH$ where a = 1 or 0 (in which case omega terminal group is H_2N-CH_2-), b = 0 - 30 and c = 0 - 30, including hydrocarbon isomers of (b) and (c), as well as hydroxylated isomers of (a), (b) and (c);

p. omega-aminoalkylsulfonic acids, $H_2N-(CH_2)_n-SO_3H$ where n = 1 - 20, such as 2-aminoethanesulfonic acid (taurine), including isomeric hydrocarbon derivatives and hydroxy or methoxy derivatives thereof;

q. omega-guanidinoalkylcarboxylic acids, of the general structure $H_2N-C(=NH)NH(CH_2)_n COOH$, where n=1-10;

r. 4-aminobenzenesulfonic acid (sulfanilic acid) and derivatives thereof, including benzene ring isomers such as 2-aminobenzene-sulfonic acid (or aniline-2-sulfonic acid) and aminoalkyl-benzene-sulfonic acids, where the aminoalkyl is $H_2N-(CH_2)_n-$, n = 1-15, as well as derivatives having more than one amino- or aminoalkyl- group;

s. sulfanilamide, $p-H_2N-C_6H_4-SO_2NH_2$, including the metabolic precursor derivatives thereof such as 4'-sulfonamido-2,4-diaminoazobenzene hydrochloride and 4'-sulfonamido-2-benzeneazo-7-acetylamino-1-hydroxynaphthalene-3,6-disulfonic acid, and the 1-amino substituted derivatives such as sulfabenz, sulfabenzamide, sulfabromomethazine, sulfacetamide, sulfachlorpyridazine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sulfamethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamoxole, sulfanilamidomethanesulfonic acid, 4-sulfanilamidosalicylic acid, 2-p-sulfanilylanilinoethanol, p-sulfanilylbenzylamine, N^4-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfanitran, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfaquinoxaline, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfazamet, sulfisomidine, sulfisoxazole, and derivatives thereof,

for controlling the symptoms of disorders selected from the

group consisting of hereditary motor and sensory neuropathies, giant axonal neuropathy, diabetic polyneuropathy and metabolic symptomology related thereto, Alzheimer's presenile dementia, Alzheimer's senile dementia, Down's syndrome, Pick's disease, Parkinson's disease, amyotrophic lateral sclerosis, and disorders clinically related thereto, Huntington's disease, tinnitus, spinal muscular atrophy, age-related atrophy of peripheral sensory and motor nerves, age-related atrophy of autonomic nerves including symptoms of hypoperistalisis of the alimentary tract, hiatal hernia (partial food regurgitation), urinary incontinence, breathing insufficiency due to diaphragm weakness and decreased autonomic sexual function, age-related atrophy of neurons of the central nervous system, age-onset pathophysiologically related changes in the cardiovascular system, kidney, optic lens and skin, including age-related skin wrinkling, Friedreich's ataxia, alcoholic polyneuropathy, multiple sclerosis, ceroid lipofuscinosis, muscular dystrophy disorders and atherosclerosis.

3. Use of a non-absorbable polyamine agent or non-absorbable polyamine-related agent or quaternary ammonium salt derivative thereof for use in the treatment of symptoms of disorders based on neurofilament associated pathology and/or pathophysiologically related symptomology.

4. Use of a non-absorbable polyamine agent or non-absorbable polyamine-related agent or quaternary ammonium salt derivative thereof selected from the group consisting of:

a. any naturally occurring polysaccharide having beta-1,3, beta-1,4 and/or beta-1,6 linkages containing aminosugars including but not limited to the chitin class of biopolymers having the group general structure of

poly-beta-(1→4)-N-acetyl-D-glucosamine

wherein such naturally occurring polysaccharide may be pretreated so as to create a microfibrillated form or microcrystalline form having enhanced surface area, increased water retention capacity and enhanced chemical accessibility such that said pretreated naturally occurring polysaccharides bear at least one free primary amine group and have a high porosity and enhanced susceptibility to chemical reactions;

b. deacetylated naturally occurring polysaccharides, having at least one N-acetylated residue, wherein upon chemical deacetylation thereof, said deacetylated naturally occurring polysaccharide is a high molecular weight derivative bearing primary amine groups directly linked to sugar carbons; including but not limited to chitosan, chondroitin sulfate, hyaluronic acid and keratan sulfate;

c. chemically aminated polysaccharides including but not limited to:

2-amino-2-deoxy-cellulose and other aminodeoxy poly-saccharides;

3-aminopropylcellulose;

aminoethylcellulose;

other aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether-, and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates including aminoalkyl derivatives such as

$$H_2N-(CH_2)_n-[carbohydrate]$$

where n = 1 - 30, including alkyl isomers;

amino(hydroxyalkyl)- derivatives such as

$$H_2N-(CH_2)_m-CHOH-(CH_2)_n-[carbohydrate]$$

where m = 0 - 15 and n = 0 - 15;

aminoalkyl-ether- derivatives and amino(hydroxyalkyl)-ether- derivatives such as

$H_2N-(CH_2)_n-O-[carbohydrate]$, where n = 1 - 30

and $H_2N-(CH_2)_m-CHOH-(CH_2)_n-O-[carbohydrate]$

where m = 0 - 15 and n = 0 - 15;

aminobenzyl derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates such as

$$H_2N-C_6H_4-(CH_2)_n-[carbohydrate]$$

and $H_2N-CH_2-C_6H_4-(CH_2)_n-[carbohydrate]$

and $H_2N-C_6H_4-(CH_2)_n-O-[carbohydrate]$ where n = 0 - 30

and $H_2N-C_6H_4-(CH_2)_m-CHOH-(CH_2)_n-O-[carbohydrate]$ where m = 0-15 and n = 0-15, including p-, o- and m-benzene ring amino- and aminomethyl- isomers, and alkyl group isomers thereof;

d. primary, secondary and tertiary amine and guanidine derivatives of sucrose polyesters including derivatives having

one or more carbonyl trapping functional group wherein the carbonyl trapping functional group is in the omega-, omega-1 or other isomeric position(s) within the fatty acyl chains;

e. synthetic polysaccharides consisting partly or entirely of aminosugars bound by beta-1,3, beta-1,4 and/or beta-1,6 linkages;

f. primary amine containing non-polysaccharide polymers which are capable of reacting with dietary carbonyl compounds including but not limited to

cholestyramine;

Bio-Rad aminex resin products such as Aminex A-14, Aminex A-25, Aminex A-27 and Aminex A-28 which are quaternary amine derivatives of 8 % crosslinked styrene divinylbenzene copolymer resin;

colestipol;

other anion exchange resins with antihypercholesterolemic properties such as Secholex (also known as polidexide, DEAE-Sephadex or PDX-Cl);

synthetic polymers having o-, m- or p-benzylammonium side chain functional groups;

and structurally related substances such as:

- weakly basic resins prepared by condensation of epichlorohydrin with ethylene imine, primary amines, secondary amines or diamines;
- other epichlorohydrin copolymers with cellulose, chitin or dextran having basic substituent functional groups such as $-OC_2H_4N(C_2H_5)_2$;
- other styrene-divinylbenzene copolymer anion exchange resins having quaternary ammonium functional groups such as

  $-CH_2N^+(CH_3)_3Cl^-$ or $-CH_2N^+(CH_3)_2CH_2CH_2OHCl^-$;
- styrene-divinylbenzene copolymer anion exchange resins having pyridinium functional groups;
- other styrene-divinylbenzene copolymer anion exchange resins having primary, secondary or tertiary amine functional groups;
- polystyrene resins having guanidine functional groups

[e.g., $-NHC(=NH)NH_2$]; and

- liquid anion exchangers containing primary amine, secondary amine, tertiary amine or quaternary salt functional groups which may be coated on particulate matrices such as cellulose, styrene-divinylbenzene copolymer or Teflon,

for controlling the symptoms of disorders selected from the group consisting of hereditary motor and sensory neuropathies, giant axonal neuropathy, diabetic polyneuropathy and metabolic symptomology related thereto, Alzheimer's presenile dementia, Alzheimer's senile dementia, Down's syndrome, Pick's disease, Parkinson's disease, amyotrophic lateral sclerosis, and disorders clinically related thereto, Huntington's disease, tinnitus, spinal muscular atrophy, age-related atrophy of peripheral sensory and motor nerves, age-related atrophy of autonomic nerves including symptoms of hypoperistalisis of the alimentary tract, hiatal hernia (partial food regurgitation), urinary incontinence, breathing insufficiency due to diaphragm weakness and decreased autonomic sexual function, age-related atrophy of neurons of the central nervous system, age-onset pathophysiologically related changes in the cardiovascular system, kidney, optic lens and skin, including age-related skin wrinkling, Friedreich's ataxia, alcoholic polyneuropathy, multiple sclerosis, ceroid lipofuscinosis, muscular dystrophy disorders and atherosclerosis.

5. The use of claim 2 characterized in that said water soluble low molecular weight substance is used in a dosage in the range of 600 mg/day to 40 grams/day.

6. The use of claim 3 characterized in that said non-absorbable polyamine agent or non-absorbable polyamine-related agent or quaternary ammonium salt derivative thereof is used in a dosage in the range of 600 mg/day to 50 grams/day.

7. The use of claim 5 characterized in that said substance is used orally.

8. The use of claim 6 characterized in that said substance is used orally.

9. The use of claim 2 characterized in that the use of

said substance is used in combination with a co-agent.

10. The use of claim 9 characterized in that the co-agent is selected from the group consisting of antioxidants, suspending reagents or the functional equivalents thereto, vitamins, hormones, chemical conjugating agents which facilitate kidney drug elimination, metabolites at risk of depletion or free radical trapping compounds.

11. The use of claim 10 characterized in that the antioxidant is selected from the group consisting of vitamin E (alpha-tocopherol), selenium, citric acid, ubiquinol, a seleno-containing amino acid, glutathione, sulfhydryl containing proteins, cysteine, homocysteine and methionine.

12. The use of Claim 10 characterized in that the suspending reagent is selected from the group consisting of carboxymethyl cellulose or functional equivalents thereof.

13. The use of claim 10 characterized in that the vitamin is selected from the group consisting of vitamin A, D, K & B-6.

14. The use of claim 10 characterized in that the hormone is selected from the group consisting of human growth hormone.

15. The use of claim 10 characterized in that the chemical conjugating agent which facilitates kidney drug elimination is selected from the group consisting of glycine and derivatives thereof.

16. The use of claim 10 characterized in that the metabolite at risk of depletion is selected from a group consisting of pantothenic acid and derivatives thereof.

17. The use of claim 9 characterized in that the co-agent is a sulfhydryl containing agent or derivative thereof such as cysteine, homocysteine, methionine or thioctic acid (alpha-lipoic acid).

18. The use of claim 10 characterized in that the co-agent is used orally.

19. The use of claim 17 characterized in that the co-agent is used orally.

20. The use of claim 2 characterized in that the substance is used intravenously.

21. The use of claim 9 characterized in that the co-agent is used intravenously.

22. Use of a water soluble, small molecular weight, primary amine containing chemical agent or amine-related derivative thereof as defined in claim 2 and/or a non-absorbable polyamine chemical agent as defined in claim 4 for controlling the symptoms of animal disorders featuring neurofilament associated pathology and/or pathophysiologically related symptomology.

23. Use of a water soluble, small molecular weight, primary amine containing chemical agent or amine-related derivative thereof as defined in claim 2 and/or a non-absorbable polyamine chemical agent as defined in claim 4,

for controlling the symptoms of animal disorders selected from a group consisting of hereditary motor and sensory neuropathies, giant axonal neuropathy, diabetic polyneuropathy and metabolic symptomology related thereto, amyotrophic lateral sclerosis, and disorders clinically related thereto, tinnitus, spinal muscular atrophy, age-related atrophy of peripheral sensory and motor nerves, age-related atrophy of autonomic nerves including symptoms of hypoperistalisis of the alimentary tract, hiatal hernia (partial food regurgitation), urinary incontinence, breathing insufficiency due to diaphragm weakness and decreased autonomic sexual function, age-related atrophy of neurons of the central nervous system, age-onset pathophysiologically related changes in the cardiovascular system, kidney, optic lens and skin, muscular dystrophy disorders and atherosclerosis.

24. Use of an agent to effectively compete with and covalently bind to disease-induced carbonyl-containing aliphatic or aromatic hydrocarbons for use in the treatment of symptoms of disorders based on neurological disease characterized by the deterioration of intracellular structures and by the spurious pathological chemical crosslinking of intracellular structures, wherein the deterioration and the crosslinking results from reaction of nerve cells and intracellular structures with disease-induced carbonyl-containing aliphatic or aromatic hydrocarbons, wherein the chemical crosslinking comprises covalent bond crosslinking of the intracellular structures.

25. The use of Claim 24 characterized in that the covalent bond crosslinking of the intracellular structures additionally

comprises a neuropathological structure(s) selected from the group consisting of:

a. polymerized aggregates of structural protein filaments such as excess neurofilament accumulation;

b. heterogeneous protein aggregates such as neurofibrillary tangles;

c. amorphous protein and lipid aggregates, such as senile plaques; and

d. lipofuscin granules.

26. The use of Claim 24 characterized in that the agent is a water soluble, small molecular weight chemical having at least one primary amine group or amine-related group thereon for reaction with carbonyl groups to yield covalently bonded products, and wherein the agent is selected from the group as defined in Claim 2.

27. The use of Claim 26 characterized in that the agent is additionally characterized in that it does not interact with the normal cell metabolism of said human or does so in a non-cytotoxic manner, is capable of being tolerated by said human in dosages in the range of 600 mg/day to 40 grams/day for extended periods of time and wherein the agent is readily absorbed by the kidney tissue and excreted in the urine without nephrotoxic consequences.

28. The use of Claim 24 characterized in that the agent comprises a non-absorbable polyamine agent or polyamine-related agent as defined in Claim 4.

29. The use of Claim 24 characterized in that the use additionally comprises use of a co-agent selected from the group consisting of antioxidants, hormones, suspending reagents, vitamins, metabolites at risk of depletion, sulfhydryl agents and chemical conjugating agents.

30. The use of Claim 28 characterized in that the use additionally comprises the use of a co-agent selected from the group consisting of antioxidants, hormones, suspending reagents, vitamins, metabolites at risk of depletion, sulfhydryl agents and chemical conjugating agents.

31. A pharmaceutical composition for use in the treatment of the symptoms of disorders selected from the group consisting

of hereditary motor and sensory neuropathies, giant axonal neuropathy, diabetic polyneuropathy and metabolic symptomology related thereto, Alzheimer's presenile dementia, Alzheimer's senile dementia, Down's syndrome, Pick's disease, Parkinson's disease, amyotrophic lateral sclerosis, and disorders clinically related thereto, Huntington's disease, tinnitus, spinal muscular atrophy, age-related atrophy of peripheral sensory and motor nerves, age-related atrophy of autonomic nerves including symptoms of hypoperistalisis of the alimentary tract, hiatal hernia (partial food regurgitation), urinary incontinence, breathing insufficiency due to diaphragm weakness and decreased autonomic sexual function, age-related atrophy of neurons of the central nervous system, age-onset pathophysiologically related changes in the cardiovascular system, kidney, optic lens and skin, including age-related skin wrinkling, Friedreich's ataxia, alcoholic polyneuropathy, multiple sclerosis, ceroid lipofuscinosis, muscular dystrophy disorders and atherosclerosis,

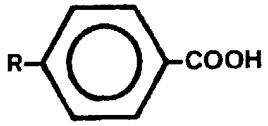
the composition comprising one or more water soluble, low molecular weight substances selected from: free acid forms, salts, benzene ring isomers, amide derivatives, carboxylic acid ester derivatives and sulfonic acid ester derivatives of the group consisting of:

a. para-aminobenzoic acid (PABA);

b. para-aminomethylbenzoic acid and analogous derivatives of the formula $H_2N-(CH_2)_n-C_6H_4-COOH$ where n = 2-30, including meta- and ortho-benzene ring isomers of the aminoalkyl group and isomers of the aminoalkyl group where the amine is not in the omega position;

c. 4-Amino-3-methylbenzoic acid and other derivatives of PABA or benzene ring isomers thereof wherein such derivatives include from one to four additional ring substituents from the group consisting of methyl group(s), ethyl group(s), or other hydrocarbon group(s) (up to 5 carbons); substituted -OH group(s) of the structure $-OCH_3$, $-C_2H_5$ or higher molecular weight ethers (up to 5 carbons); substituted amine group(s) of the structure -NHR, $-NR_2$ or -NHCOR where R is a hydrocarbon substituent such as $-CH_3$ or derivative thereof (R having 1 to 5 carbons);

d. 4-amidinobenzoic acid, $H_2N-C(=NH)C_6H_4-COOH$, and the following derivatives thereof:



where R= $-NHC(=NH)NH_2$
or $CH_2NHC(=NH)NH_2$
or $(CH_2)_nNHC(=NH)NH_2$
where n = 2 - 10;

e. para-aminophenylacetic acid and analogous derivatives of the formula $H_2N-(CH_2)_n-C_6H_4-CH_2-COOH$ where n = 1-30, as well as methyl and other sidechain hydrocarbon isomers of the amino-alkyl group, and/or hydroxylated derivatives of the sidechain aminoalkyl group, and/or derivatives bearing hydrocarbon or hydroxyl substitutions at the alpha carbon of the acetate group;

f. 4-amidinophenylacetic acid, $H_2N-C(=NH)C_6H_4-CH_2-COOH$;

g. para-aminohippuric acid, $H_2N-C_6H_4-CO-NH-CH_2-COOH$;

h. 3,5-diaminobenzoic acid and other benzene ring diamine isomers;

i. 3,5-diaminoalkylbenzoic acid and benzene ring isomers, where aminoalkyl is $H_2N-(CH_2)_n-$ and n = 1 - 30, including hydrocarbon isomers, or where aminoalkyl is

$$H_2N-(CH_2)_m-CHOH-(CH_2)_n-$$

where m = 0 - 15 and n = 0 - 15, including hydrocarbon isomers thereof;

j. para-aminosalicylic acid, and the isomeric amine and hydroxyl derivatives thereof, as well as derivatives wherein the hydroxyl group has been replaced by a methoxy group or alkyloxy group having 2-10 carbons;

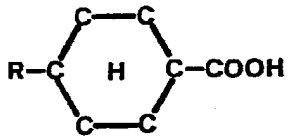
k. 4-amino-2-sulfobenzoic acid, and derivaties thereof including benzene ring isomers and derivatives where the amino group is re-placed by an aminoalkyl group having 1-10 carbons, and derivatives where the carboxylic acid group is replaced by a $-(CH_2)_n-COOH$ group (n=1-10);

l. 6-aminonicotinic acid and the ring isomer derivatives thereof;

m. epsilon-aminocaproic acid, and analogous remaining derivatives of the formula $H_2N-(CH_2)_n-COOH$, where n = 1-30, including isomers wherein the amine is not in the omega position as well as derivatives wherein the alkyl group bears sidechain

methyl or other hydrocarbon substitutions and/or hydroxyl group substitutions thereon;

n. tranexamic acid, 4-(aminomethyl)cyclohexane-carboxylic acid, and the ring positional isomers thereof, and derivatives



wherein R= $-NH_2$

$-(CH_2)_n NH_2$

where n=2-10

$-NHC(=NH)NH_2$

$-CH_2 NHC(=NH)NH_2$

$-(CH_2)_n NHC(=NH)NH_2$

where n = 2 - 10;

o. 2,3-diaminopropionic acid and analogous derivatives of the formula $(H_3C)_a-CHNH_2-(CH_2)_b-CHNH_2-(CH_2)_c-COOH$ where a = 1 or 0 (in which case omega terminal group is H_2N-CH_2-), b = 0 - 30 and c = 0 - 30, including hydrocarbon isomers of (b) and (c), as well as hydroxylated isomers of (a), (b) and (c);

p. omega-aminoalkylsulfonic acids, $H_2N-(CH_2)_n-SO_3H$ where n = 1 - 20, such as 2-aminoethanesulfonic acid (taurine), including isomeric hydrocarbon derivatives and hydroxy or methoxy derivatives thereof;

q. omega-guanidinoalkylcarboxylic acids, of the general structure $H_2N-C(=NH)NH(CH_2)_n COOH$, where n=1-10;

r. 4-aminobenzenesulfonic acid (sulfanilic acid) and derivatives thereof, including benzene ring isomers such as 2-aminobenzene-sulfonic acid (or aniline-2-sulfonic acid) and aminoalkyl-benzene-sulfonic acids, where the aminoalkyl is $H_2N-(CH_2)_n-$, n = 1-15, as well as derivatives having more than one amino- or aminoalkyl- group;

s. sulfanilamide, $p-H_2N-C_6H_4-SO_2NH_2$, including the metabolic precursor derivatives thereof such as 4'-sulfonamido-2,4-diaminoazobenzene hydrochloride and 4'-sulfonamido-2-benzeneazo-7-acetylamino-1-hydroxynaphthalene-3,6-disulfonic acid, and the 1-amino substituted derivatives such as sulfabenz, sulfabenzamide, sulfabromomethazine, sulfacetamide, sulfachlorpyridazine, sulfacytine, sulfadiazine, sulfadicramide, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguanidine, sulfaguanole, sulfalene, sulfamerazine, sulfameter, sulfamethazine, sulfamethizole, sul-

famethomidine, sulfamethoxazole, sulfamethoxypyridazine, sulfamethylthiazole, sulfametrole, sulfamoxole, sulfanilamidomethanesulfonic acid, 4-sulfanilamidosalicylic acid, 2-p-sulfanilylanilinoethanol, p-sulfanilylbenzylamine, N^4-sulfanilylsulfanilamide, sulfanilylurea, N-sulfanilyl-3,4-xylamide, sulfanitran, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfaquinoxaline, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiourea, sulfazamet, sulfisomidine, sulfisoxazole, and derivatives thereof,

in a dosage rate of from 600 milligrams/day to 40 grams/day, in association with a pharmaceutically acceptable carrier thereof.

32. The composition of claim 31 additionally comprising a co-agent.

33. The composition of claim 32 wherein the co-agent is selected from the group consisting of antioxidants, suspending reagents or the functional equivalents thereto, vitamins, hormones, chemical conjugating agents which facilitate kidney drug elimination, metabolites at risk of depletion or free radical trapping compounds.

34. A pharmaceutical composition for use in the treatment of the symptoms of disorders selected from the group consisting of hereditary motor and sensory neuropathies, giant axonal neuropathy, diabetic polyneuropathy and metabolic symptomology related thereto, Alzheimer's presenile dementia, Alzheimer's senile dementia, Down's syndrome, Pick's disease, Parkinson's disease, amyotrophic lateral sclerosis, and disorders clinically related thereto, Huntington's disease, tinnitus, spinal muscular atrophy, age-related atrophy of peripheral sensory and motor nerves, age-related atrophy of autonomic nerves including symptoms of hypoperistalisis of the alimentary tract, hiatal hernia (partial food regurgitation), urinary incontinence, breathing insufficiency due to diaphragm weakness and decreased autonomic sexual function, age-related atrophy of neurons of the central nervous system, age-onset pathophysiologically related changes in the cardiovascular system, kidney, optic lens and skin, including age-related skin wrinkling, Friedreich's ataxia, alco-

holic polyneuropathy, multiple sclerosis, ceroid lipofuscinosis, muscular dystrophy disorders and atherosclerosis,

the composition comprising one or more non-absorbable polyamine agent or non-absorbable polyamine-related agent or quaternary ammonium salt derivatives thereof selected from the group consisting of:

a. any naturally occurring polysaccharide having beta-1,3, beta-1,4 and/or beta-1,6 linkages containing aminosugars including but not limited to the chitin class of biopolymers having the general structure of

poly-beta-(1→4)-N-acetyl-D-glucosamine

wherein such naturally occurring polysaccharide may be pretreated so as to create a microfibrillated form or microcrystalline form having enhanced surface area, increased water retention capacity and enhanced chemical accessibility such that said pretreated naturally occurring polysaccharides bear at least one free primary amine group and have a high porosity and enhanced susceptibility to chemical reactions;

b. deacetylated naturally occurring polysaccharides, having at least one N-acetylated residue, wherein upon chemical deacetylation thereof, said deacetylated naturally occurring polysaccharide is a high molecular weight derivative bearing primary amine groups directly linked to sugar carbons; including but not limited to chitosan, chondroitin sulfate, hyaluronic acid and keratan sulfate;

c. chemically aminated polysaccharides including but not limited to:

2-amino-2-deoxy-cellulose and other aminodeoxy polysaccharides;

3-aminopropylcellulose;

aminoethylcellulose;

other aminoalkyl-, amino(hydroxyalkyl)-, aminoalkyl-ether-, and amino(hydroxyalkyl)-ether- derivatives of cellulose, chitin and other naturally occurring non-digestible carbohydrates including aminoalkyl derivatives such as

$$H_2N-(CH_2)_n-[\text{carbohydrate}]$$

where n = 1 - 30, including alkyl isomers;

amino(hydroxyalkyl)- derivatives such as

$$H_2N-(CH_2)_m-CHOH-(CH_2)_n-[carbohydrate]$$

where m = 0 - 15 and n = 0 - 15;

aminoalkyl-ether- derivatives and amino(hydroxyaklyl)-ether- derivatives such as

$$H_2N-(CH_2)_n-O-[carbohydrate]$$

where n = 1 - 30 and

$$H_2N-(CH_2)_m-CHOH-(CH_2)_n-O-[carbohydrate]$$

where m = 0 - 15 and n = 0 - 15;

aminobenzyl derivatives of cellulose, chitin or other naturally occurring non-digestible carbohydrates such as

$$H_2N-C_6H_4-(CH_2)_n-[carbohydrate]$$

and $H_2N-CH_2-C_6H_4-(CH_2)_n-[carbohydrate]$

and $H_2N-C_6H_4-(CH_2)_n-O-[carbohydrate]$ where n = 0 - 30

and $H_2N-C_6H_4-(CH_2)_m-CHOH-(CH_2)_n-O-[carbohydrate]$

where m = 0-15 and n = 0-15, including p-, o- and m-benzene ring amino- and aminomethyl- isomers, and alkyl group isomers thereof;

d. primary, secondary and tertiary amine and guanidine derivatives of sucrose polyesters including derivatives having one or more carbonyl trapping functional group wherein the carbonyl trapping functional group is in the omega-, omega-1 or other isomeric position(s) within the fatty acyl chains;

e. synthetic polysaccharides consisting partly or entirely of aminosugars bound by beta-1,3, beta-1,4 and/or beta-1,6 linkages;

f. primary amine containing non-polysaccharide polymers which are capable of reacting with dietary carbonyl compounds including but not limited to

cholestyramine;

Bio-Rad aminex resin products such as Aminex A-14, Aminex A-25, Aminex A-27 and Aminex A-28 which are quaternary amine derivatives of 8 % crosslinked styrene divinylbenzene copolymer resin;

colestipol;

other anion exchange resins with antihypercholesterolemic properties such as Secholex (also known as polidexide, DEAE-

Sephadex or PDX-C1);

synthetic polymers having o-, m- or p-benzylammonium side chain functional groups;

and structurally related substances such as:

- weakly basic resins prepared by condensation of epichlorohydrin with ethylene imine, primary amines, secondary amines or diamines;
- other epichlorohydrin copolymers with cellulose, chitin or dextran having basic substituent functional groups such as $-OC_2H_4N(C_2H_5)_2$;
- other styrene-divinylbenzene copolymer anion exchange resins having quaternary ammonium functional groups such as $-CH_2N^+(CH_3)_3Cl^-$ or $-CH_2N^+(CH_3)_2CH_2CH_2OHCl^-$;
- styrene-divinylbenzene copolymer anion exchange resins having pyridinium functional groups;
- other styrene-divinylbenzene copolymer anion exchange resins having primary, secondary or tertiary amine functional groups;
- polystyrene resins having guanidine functional groups [e.g., $-NHC(=NH)NH_2$]; and
- liquid anion exchangers containing primary amine, secondary amine, tertiary amine or quaternary salt functional groups which may be coated on particulate matrices such as cellulose, styrene-divinylbenzene copolymer or Teflon, and pharmaceutically active derivatives thereof,

in a dosage rate of from 600 milligrams/day to 50 grams/day, in association with a pharmaceutically acceptable carrier thereof.

35. Use of a trapping compound to inhibit rancidity in a food product and extend the shelf life of the food product by trapping and deactivating carbonyl products generated from sugars in the food product, by admixing the food product with the trapping compound, wherein the trapping compound is a small molecular weight amine or amine-related agent selected from the group thereof set forth in claim 2.

36. Use of a trapping compound to inhibit rancidity in a food product and extend the shelf life of the food product by

trapping and deactivating carbonyl products generated from sugars in the food product, wherein the carbonyl product which is trapped and deactivated is a Maillard reaction aldehyde precursor or chemically related furan derivative, and wherein the use comprises liquefying the food product, passing the liquified food product through a sieve comprising a non-absorbable polyamine or polyamine-related carbonyl trapping agent selected from the group consisting of non-absorbable carbohydrates, sucrose polyesters and synthetic plastic resins having primary amine groups or derivatives thereof.

37. The use of claim 36 wherein the non-absorbable polyamine or polyamine-related carbonyl trapping agent is selected from a group consisting of those chemical agents and compounds set forth in claim 4.

38. Use of a trapping compound to inhibit rancidity in a food product and extend the shelf life of the food product by trapping and deactivating carbonyl products generated from sugars in the food product in the course of processing the food product, wherein the carbonyl product is a Maillard reaction aldehyde precursor or chemically related furan derivative, the use comprising:

(a) liquefying the food product;

(b) mixing the liquified food product for a predetermined time period with a particulate form of one or more non-absorbable polyamine or polyamine-related carbonyl trapping agents selected from the group consisting of non-absorbable carbohydrates, sucrose polyesters and synthetic plastic resins having primary amine groups or derivatives thereof to form a mixture thereof;

(c) centrifuging the mixture for a predetermined time period; and

(d) separating the liquid food product from the mixture.

39. The use of claim 38 characterized in that the non-absorbable polyamine or polyamine-related carbonyl trapping agent is selected from a group consisting of the chemical agents and compounds set forth in claim 4.

40. The use of claim 35 characterized in that the carbonyl products in the food product are selected from the group con-

sisting of furanaldehydes, and other aldehyde and/or ketone containing compounds, wherein the food products are treated so that they may be regarded as more healthful and promote the health of those consuming the food products and so that the food products may be publicly described as generally furanaldehyde free, aldehyde free or reduced aldehyde.

41. The use of claim 37 characterized in that the carbonyl products in the food product are selected from the group consisting of furanaldehydes, and other aldehyde and/or ketone containing compounds, wherein the food products are treated so that they may be regarded as more healthful and promote the health of those consuming the food products and so that the food products may be publicly described as generally furanaldehyde free, aldehyde free or reduced aldehyde.

42. Use of a water soluble, low molecular weight substance (100 to 1,00 range of molecular weights) selected from the group consisting of those chemical agents and compounds set forth in claim 2, for effecting the slowing of skin aging and improving the appearance of skin, by topically using the substance in association with a pharmaceutically acceptable carrier thereof.

43. A pharmaceutical composition for use in the treatment of the symptoms of skin aging, the composition comprising one or more of the chemical agents and compounds set forth in claim 2, in association with a pharmaceutically acceptable carrier thereof.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/01365

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61K 31/34,31/505,31/54,31/165,37/54,9/06
US CL : 514/267,21,866,619,885,846,567;536/20;435/808;524/29

II. FIELDS SEARCHED

Minimum Documentation Searched[4]

Classification System	Classification Symbols
U.S.	514/267,21,866,619,885,846,567;536/20;435/808;524/29

Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched[6]

APS

III. DOCUMENTS CONSIDERED TO BE RELEVANT[14]

Category*	Citation of Document,[16] with indication, where appropriate, of the relevant passages[17]	Relevant to Claim No.[18]
Y	US,A, 4,665,069 (Rosenburg) 12 May 1987, column 5, lines 1-12.	1-43
Y	US,A, 4,638,014 (Clark) 20 January 1987, column 12,lines 8-20.	1-43
Y	US,A, 4,889,722 (Sheffield et al) 26 December 1989, columns 3,lines 64-68 and 4 lines 1-37, and claims 1-15.	1-43
Y	US,A, 4,309,534 (Austin) 05 January 1982, column 6,lines 27-36.	1-43
Y	Tortora & Angnostakos, "Principles of Anatomy & Physiology " 2nd Edition, published 1975 by Harper & Row Publishers Inc. See pages 394 and 589.	10-20
Y	Zubay, "Biochemistry" published 1983 by the Benjamin/Cummings Publishing Company, Inc. See pages 565,1104-1109 and 1115.	10-20
Y	US,A, 4,595,586 (Flom) 17 June 1986, see entire document.	1-43
A,P	US,A, 5,013,769 (Murray et al) 07 May 1991.	1-43
A	US,A, 4,154,850 (Morgan et al) 15 May 1979.	1-43

* Special categories of cited documents:[15]

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search[2]	Date of Mailing of this International Search Report[2]
02 JUNE 1992	22 JUN 1992
International Searching Authority[1]	Signature of Authorized Officer[20]
ISA/US	LOUISE N. LEARY

Form PCT/ISA/210 (second sheet)(May 1986) *

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

A	US,A, 4,812,447 (Roberts) 14 March 1989.	1-43
A	US,A, 4,923,696 (Appel et al) 08 May 1990.	1-43
A	US,A, 4,039,388 (Gal et al) 02 August 1977.	1-43

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE[1]

1. ☐ Claim numbers _, because they relate to subject matter (1) not required to be searched by this Authority, namely:

2. ☐ Claim numbers _, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out (1), specifically:

3. ☐ Claim numbers _, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING[2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Search Authority did not invite payment of any additional fee.

Remark on protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.